HIV 1/O/2 Enhanced (EHIV)

Assay for the Detection of Antibodies to Human Immunodeficiency Virus Type 1, Including Group O (HIV-1 + "O") and/or Type 2 (HIV-2)

Assay Summary

Sample Type	*Serum, Potassium EDTA plasma, Lithium or Sodium Heparinized plasma, ACD*
Sample Volume	*50 µL*
Calibrator	*EHIV*
Assay Range	*0.05 – 50.00 Index*

Contents

REF	*Contents*	*Number of Tests*
01622429	1 ReadyPack® primary reagent pack containing ADVIA Centaur® EHIV Solid Phase, Lite Reagent, and Ancillary Lite Reagent ADVIA Centaur EHIV Master Curve card 1 vial EHIV Low Calibrator CAL L 1 vial EHIV High Calibrator CAL H ADVIA Centaur EHIV Calibrator Assigned Value card 1 vial EHIV Negative Control CONTROL – 1 vial EHIV Positive Control 1 CONTROL 1 + 1 vial EHIV Positive Control 2 CONTROL 2 + 1 vial EHIV Positive Control 3 CONTROL 3 + Expected Control Value cards	200

For a definition of symbols used in product labeling, please refer to Appendix D, *Understanding the Symbols,* in the *ADVIA Centaur® Assay Manual*.

Intended Use

The ADVIA Centaur HIV 1/O/2 Enhanced assay is an *in vitro* diagnostic immunoassay for the qualitative determination of antibodies to the human immunodeficiency virus type 1, including Group O, and/or type 2 in serum or plasma (potassium EDTA, lithium or sodium heparinized, or ACD) using the ADVIA Centaur System.

This product is not intended for testing or screening pooled specimens from more than one individual, or for use in screening blood or plasma donors. Purchase of this product does not convey any right or license under any relevant patents to use the product for testing or screening pooled blood specimens from more than one individual or for use in screening blood or plasma donors.

WARNING: This assay and the ADVIA Centaur System are not FDA cleared or approved for use in screening blood or plasma donors.

CAUTION: United States federal law restricts this device to sale by or on the order of a physician.

Materials Required But Not Provided

REF	Description	Contents
09973131	Bayer HealthCare ADVIA Centaur System	
01137199 (112351)	Bayer HealthCare ADVIA Centaur Wash 1 WASH	2 x 1500 mL/pack

Summary and Explanation of the Test

The ADVIA Centaur HIV 1/O/2 Enhanced assay is an antigen bridging microparticle chemiluminometric immunoassay used for the detection of antibodies to the human immunodeficiency virus type 1, including Group O, and/or type 2 in serum or plasma.

Human immunodeficiency virus is the causative agent of acquired immunodeficiency syndrome (AIDS). AIDS was first described in the United States in 1981 and has become one of the leading causes of death worldwide. Despite educational efforts directed towards reducing the transmission of AIDS and increased advancements in treatment, the number of AIDS cases continues to increase. By the year 2010, it is estimated that there will be at least 45 million new human immunodeficiency virus (HIV) infections worldwide. [1,2,]

Human immunodeficiency virus type 1 (HIV-1) has been identified as the primary cause of acquired immunodeficiency syndrome (AIDS). This retrovirus, a member of the lentivirinae subfamily, is spread by sexual contact, exposure to infected blood or blood products, and perinatal transmission. In 1986 human immunodeficiency virus type 2 (HIV-2) was isolated from AIDS patients in West Africa. These viruses share epitopes of the core proteins, but exhibit little or no cross-reactivity between the envelope glycoproteins.[3,4]

Comparison of the nucleic acid sequences for HIV-1 and HIV-2 shows approximately 60% homology in the conserved genes, such as *gag* and *pol* (encoding core proteins), and 30 to 40% homology in less conserved regions (encoding envelope proteins). HIV-1 has been subdivided into group M (subtypes A-H) and Group O.[5]

The routes of transmission of HIV-1 and HIV-2 are the same, however in HIV-2 infections the transmission and the viral replication rate are much lower. Clinical studies have shown that in HIV-2 infections there is a slower disease progression than in HIV-1 infections. In HIV-2 infections there is a slower rate in the decline of CD4 T cells and reduced viremia. Individuals infected with HIV-2 generally have a better clinical outcome.[4,6]

The ADVIA Centaur HIV 1/O/2 Enhanced assay uses yeast recombinant derived antigens corresponding to the viral envelope and core proteins. Recombinant antigens include an HIV-1 envelope protein (gp41/120), an HIV-1 core protein (p24), and an HIV-2 envelope protein (gp36). A synthetic peptide is added for the detection of antibodies to HIV-1 group O.

The primary purpose of the ADVIA Centaur HIV 1/O/2 Enhanced assay is to aid in the diagnosis of HIV infection and AIDS. Specimens that are initially reactive should be retested in duplicate. Repeat reactivity is highly predictive of the presence of antibody to HIV-1 and/or HIV-2 in specimens from people at risk for HIV infection, and should be followed-up with appropriate supplemental tests for HIV-1 and HIV-2 antibody before making a diagnosis of HIV infection.

Assay Principle

The ADVIA Centaur HIV 1/O/2 Enhanced assay is a two-wash antigen sandwich immunoassay in which antigens are bridged by antibody present in the patient sample. The Solid Phase contains a preformed complex of streptavidin coated paramagnetic microparticles and biotinylated HIV-1 and HIV-2 recombinant antigens and Group O peptide antigen. This reagent is used to capture anti-HIV-1 and/or HIV-2 antibodies in the specimen. The Ancillary Lite Reagent and Lite Reagent contain acridinium ester labeled HIV-1 and HIV-2 recombinant antigens and Group O peptide antigen used to detect anti-HIV-1 and/or HIV-2 antibodies bound to the Solid Phase in the sample.

The system automatically performs the following steps:

- dispenses 50 µL of specimen into a cuvette and incubates for 6 minutes at 37°C
- dispenses 100 µL of Solid Phase and 50 µL of Ancillary Lite Reagent and incubates for 18 minutes at 37°C
- separates the Solid Phase from the mixture and aspirates the unbound reagent
- washes the cuvette with Wash 1
- dispenses 50 µL of Lite Reagent, incubates the mixture for 18 minutes at 37°C
- separates the Solid Phase from the mixture and aspirates unbound reagent
- washes the cuvette with Wash 1
- dispenses 300 µL each of Acid Reagent and Base Reagent* to initiate the chemiluminescent reaction
- reports results in index values

A direct relationship exists between the amount of HIV 1/O/2 antibody activity present in the specimen and the amount of relative light units (RLUs) detected by the system. A result of reactive or nonreactive is determined according to the Index Value established with the calibrators. Refer to *Interpretation of Results* for a description of the Cutoff Value calculation.

* components required for use in running the ADVIA Centaur System

Specimen Collection and Handling

Serum, potassium EDTA plasma, lithium or sodium heparinized plasma, and ACD plasma are the recommended specimen types for this assay. Do not use specimens with obvious microbial contamination. The performance of the ADVIA Centaur HIV 1/O/2 Enhanced assay has not been established with cord blood, neonatal specimens, cadaver specimens, heat-inactivated specimens, or body fluids other than serum or plasma such as saliva, urine, amniotic, or pleural fluid.

The following general recommendations for handling and storing blood specimens are furnished by the Clinical Laboratory and Standards Institute (CLSI, formerly NCCLS),[7] and augmented with additional sample handling studies:

- Handle all specimens as if capable of transmitting disease.
- Specimens are processed by centrifugation, typically followed by physical separation of the serum or plasma from the red cells. The centrifugation step may occur up to 24 hours post draw.
- Test specimens as soon as possible after collecting. Store specimens at 2° to 8°C if not tested within 24 hours of collection.

- Store specimens stoppered and upright at all times at 2° to 8°C up to 14 days.
- Freeze specimens, devoid of red blood cells, at or below -20°C for longer storage. Specimens may be stored at or below -20°C for up to 365 days with the exception of specimens collected in EDTA plastic, lithium heparin glass and plastic, and SST plastic tube types which may be stored at or below -20°C for up to 168 days. Do not store in a frost-free freezer. When 10 specimens were subject to 6 freeze/thaw cycles, no clinically significant differences were observed. Thoroughly mix thawed specimens and centrifuge at 10,000xg for 2 min before using.
- Package and label specimens for shipment in compliance with applicable federal and international regulations covering the transport of clinical specimens and etiological agents. Specimens maintained at room temperature up to 24 hours or refrigerated up to 14 days demonstrated no clinically significant differences. Store specimens stoppered and upright at 2° to 8°C upon arrival. If shipment is expected to be subjected to temperatures above 25°C, ship specimens frozen.
- Specimens may be stored in primary tubes up to 5 days at 2° to 8°C. Primary tube specimens include serum stored on the clot, plasma stored on packed red cells, and specimens processed and stored in gel barrier blood collection tubes. When 10 specimens in these primary tubes were tested up to 5 days, no clinically significant differences were observed.
- Specimens may be stored on the ADVIA Centaur System for 8 hours.

Before placing specimens on the system, ensure the following:

- Specimens are free of fibrin or other particulate matter. Remove particulates by centrifugation. (Example: 1500xg for 10 minutes; follow tube manufacturer's recommendations.)
- Specimens are free of bubbles or foam.

NOTE: Negative specimens collected in sodium or lithium heparin may have elevated index values compared to serum. This could result in some high negative specimens in lithium or sodium heparin appearing reactive.

Reagents

Store the reagents upright at 2–8°C.

Mix all primary reagent packs by hand before loading them onto the system. Visually inspect the bottom of the reagent pack to ensure that all particles are dispersed and resuspended. For detailed information about preparing the reagents for use, refer to Appendix C, *Handling Reagents* in the ADVIA *Centaur Assay Manual*.

Keep away from sunlight. Protect reagent packs from all light sources. Reagent packs loaded on the system are protected from light. Store unused reagent packs at 2–8°C away from light sources.

Reagent	*Component*	*Volume*	*Ingredients*	*Storage*	*Stability*
ADVIA Centaur HIV ReadyPack primary reagent pack	Solid Phase	20.0 mL/ reagent pack	streptavidin coated paramagnetic microparticles preformed with biotinylated HIV antigens (~1.0 µg/mL) in buffer with bovine serum albumin, goat serum, surfactant, and preservatives.	2-8°C	Stable until the expiration date on the pack label. For onboard stability, refer to *Onboard Stability and Calibration Interval.*
	Lite Reagent	10.0 mL/ reagent pack	recombinant HIV antigens (~0.50 µg/mL) labeled with acridinium ester in buffer with bovine serum albumin, mouse IgG, goat serum, surfactant, and preservatives	2-8°C	Stable until the expiration date on the pack label. For onboard stability, refer to *Onboard Stability and Calibration Interval.*
	Ancillary Lite Reagent	10.0 mL/ reagent pack	recombinant HIV antigens (~0.50 µg/mL) labeled with acridinium ester in buffer with bovine serum albumin, mouse IgG, goat serum, surfactant, and preservatives	2-8°C	Stable until the expiration date on the pack label. For onboard stability, refer to *Onboard Stability and Calibration Interval.*
HIV calibrator vials	Calibrators	2.0 mL/ vial	Processed** human plasma negative for antibodies to HIV spiked with antibodies to HIV-1, sodium azide (<0.1%) and preservatives	2-8°C	Stable until the expiration date on the vial or onboard–8 hours
HIV control vials***	Controls	7.0 mL/ vial	Processed** human plasma nonreactive for HIV, reactive for HIV-1, and reactive for HIV-2 with sodium azide (<0.1%) and preservatives, processed** goat plasma reactive for HIV-1 Group "O" with sodium azide (<0.1%) and preservatives	2-8°C	Stable until the expiration date on the vial or onboard–8 hours
ADVIA Centaur WASH 1*	Wash 1	1500 mL/ pack	phosphate buffered saline with sodium azide (< 0.1%) and surfactant	2-25°C	Stable until the expiration date on the vial or onboard–14 days

* See *Materials Required But Not Provided*

** Processed plasma is defibrinated and filtered plasma

*** EHIV Negative Control
EHIV Positive Control 1 (HIV-1 antibodies)
EHIV Positive Control 2 (HIV-2 antibodies)
EHIV Positive Control 3 (HIV-1 Group "O" antibodies)

Precautions and Warnings

For *In Vitro* Diagnostic Use.

NOTE: Sodium azide can react with copper and lead plumbing to form explosive metal azides. On disposal, flush reagents with a large volume of water to prevent the buildup of azides, if disposal into a drain is in compliance with federal, state, and local requirements.

R43 **Irritant!** May cause sensitization by skin contact. Avoid contact with skin. Wear suitable gloves.
S24 **Contains:** 5-chloro-2-methyl-2H-isothiazol-3-one and 2-methyl-2H-isothiazol-3-one; Calibrators,
S37 Controls.

CAUTION! POTENTIAL BIOHAZARD: Some components of this product contain human source material. No known test method can offer complete assurance that products derived from human blood will not transmit infectious agents. All products manufactured using human source material should be handled as potentially infectious. Handle this product according to established good laboratory practices and universal precautions.[8-10]
The negative control has been assayed by FDA-approved methods and found to be nonreactive for hepatitis B virus, antibody to HCV, and antibody to HIV-1/2. The positive controls, low calibrator and high calibrator have been assayed by FDA-approved methods and found to be nonreactive for hepatitis B virus and antibody to HCV. The positive controls, low calibrator, and high calibrator contain human plasma that is reactive for antibody to HIV. The units were treated with a BPL-UV inactivation procedure,[11] however, all products manufactured using human source material should be handled as potentially infectious.

CAUTION**:** This device contains material of animal origin and should be handled as a potential carrier and transmitter of disease.

Loading Reagents

Ensure that the system has sufficient primary reagent packs. For detailed information about preparing the system, refer to the system operating instructions or to the online help system.

Mix all primary reagent packs by hand before loading them onto the system. Visually inspect the bottom of the reagent pack to ensure that all particles are dispersed and resuspended. For detailed information about preparing the reagents for use, refer to Appendix C, *Handling Reagents*, in the *ADVIA Centaur Assay Manual*.

Load the ReadyPack primary reagent packs in the primary reagent compartment using the arrows on the packs as a placement guide. The system automatically mixes the primary reagent packs to maintain homogeneous suspension of the reagents. For detailed information about loading reagents, refer to the system operating instructions or to the online help system.

NOTE: The Low and High Calibrators provided in this kit are matched to the ReadyPack primary reagent pack. Do not mix calibrator lots with different lots of reagent packs.

Onboard Stability and Calibration Interval

Onboard Stability	Calibration Interval
28 days	14 days

NOTE: Remove the packs from the ADVIA Centaur and gently resuspend the packs during the weekly maintenance schedule. Refer to Appendix C in the *ADVIA Centaur Assay Manual.*

Additionally, the ADVIA Centaur HIV 1/O/2 Enhanced assay requires a two-point calibration:

- when changing lot numbers of primary reagent packs
- when replacing system components
- when quality control results are repeatedly out of range

NOTE:

- Discard reagent packs at the end of the onboard stability interval.
- Do not use reagents beyond the expiration date.

Master Curve Calibration

The ADVIA Centaur HIV 1/O/2 Enhanced assay requires a Master Curve calibration when using a new lot number of Lite Reagent, Solid Phase, and Ancillary Lite Reagent. For each new lot number of Lite Reagent, Solid Phase, and Ancillary Lite Reagent, use the barcode reader or keyboard to enter the Master Curve values on the system. The Master Curve card contains the Master Curve values. For detailed information about entering calibration values, refer to the system operating instructions or to the online help system.

Calibration

For calibration of the ADVIA Centaur HIV 1/O/2 Enhanced assay, use EHIV Calibrators provided with each kit. The calibrators provided in this kit are matched to the ReadyPack primary reagent pack.

Using Barcode Labels

NOTE: Calibrator barcode labels are lot number specific. Do not use barcode labels from one lot of calibrators with any other lot of calibrators.

Use the ADVIA Centaur HIV 1/O/2 Enhanced Calibrator barcode labels to identify the Low and High Calibrator sample cups when performing the ADVIA Centaur HIV 1/O/2 Enhanced assay. Place the barcode label on the sample cup so that the readable characters on the side of the label are vertical on the sample cup.

Performing a Calibration

Each lot of calibrators contains a Calibrator Assigned Value card to facilitate entering the calibration values on the system. Enter the values using the barcode scanner or the keyboard. For detailed information about entering calibrator values, refer to the system operating instructions or to the online help system.

NOTE: This procedure uses calibrator volumes sufficient to measure each calibrator in duplicate.

1. Schedule the calibrators to the worklist.
2. Label two sample cups with calibrator barcode labels: one for the low and another for the high.

NOTE: Each drop from the calibrator bottle is approximately 50 µL.

3. Gently mix the Low and High Calibrators and dispense at least 4 to 5 drops of each calibrator into the appropriate sample cups.
4. Load the sample cups in a rack.
5. Place the rack in the sample entry queue.
6. Ensure that the assay reagents are loaded.
7. Start the entry queue, if required.

NOTE: Dispose of any calibrator remaining in the sample cups after 8 hours. Do not refill sample cups when the contents are depleted; if required, dispense fresh calibrators.

Quality Control

The ADVIA Centaur HIV 1/O/2 Enhanced assay has the added feature of control bracketing. The four controls supplied in the assay kit must be assayed before and after a specimen or group of specimens. Specimen results are suppressed until it is determined that all control replicates are within expected ranges. This feature is designed to operate in the full random access capability of the ADVIA Centaur System. Refer to Operating Document 078D0383 for full details and procedures for control bracketing.

For quality control of the ADVIA Centaur HIV 1/O/2 Enhanced assay, use EHIV controls. The controls provided in this kit are matched to the ReadyPack primary reagent pack. Refer to the Expected Value cards for the suggested expected values specific for the lot number of the positive and negative controls.

Using Barcode Labels

NOTE: Control barcode labels are lot number specific. Do not use barcode labels from one lot of controls with any other lot of controls.

Use the ADVIA Centaur EHIV quality control barcode labels to identify the positive and negative specimen cups when performing the ADVIA Centaur HIV 1/O/2 Enhanced assay. Place the barcode label on the specimen cup so that the readable characters on the side of the label are vertical on the specimen cup.

Performing Quality Control

For detailed information about entering quality control values using the Expected Control Value cards, refer to the system operating instructions or to the online help system.

NOTE: The four controls supplied in the assay kit are required to open and close the control bracket and to report results.

Treat all quality control samples the same as specimens.

NOTE: This procedure uses control volumes sufficient to measure each control in duplicate.

1. Schedule the quality control samples on the worklist.
2. Label four sample cups with quality control barcode labels: one for each positive, and one for the negative.

NOTE: Each drop from the control vial is approximately 50 µL.

3. Gently mix the quality control materials and dispense at least 4 to 5 drops of each control into the appropriate sample cups.
4. Load the sample cups in a rack.
5. Place the rack in the sample entry queue.
6. Ensure that the assay reagents are loaded.
7. Start the entry queue, if required.

NOTE: Dispose of any quality control materials remaining in the sample cups after 8 hours. Do not refill sample cups when the contents are depleted; if required, dispense fresh quality control materials.

Taking Corrective Action

If the quality control results do not fall within the values specified on the Expected Control Value cards, then do the following:

- investigate and determine the cause for the unacceptable control results
- review these instructions to ensure that the assay was performed according to the procedures recommended by Bayer HealthCare.
- verify that the materials are not expired.
- verify that required maintenance was performed.
- if necessary contact Bayer HealthCare for more assistance.
- when the condition is corrected, retest specimens and controls.

Specimen Volume

This assay requires 50 µL of specimen for a single determination. This volume does not include the unusable volume in the specimen container or the additional volume required when performing duplicates or other tests on the same specimen. For detailed information about determining the minimum required volume, refer to *Sample Volume Requirements* in the *ADVIA Centaur Reference Manual.*

Assay Procedure

For detailed procedural information, refer to the system operating instructions or to the online help system.

CAUTION: Do not load more than one size of specimen container in each rack. The rack indicator must be positioned at the correct setting for the size of specimen container.

1. Prepare the specimen container for each specimen, and place barcode labels on the specimen containers, as required.
2. Load each specimen container into a rack, ensuring that the barcode labels are clearly visible.
3. Place the racks in the entry queue.
4. Ensure that the assay reagents are loaded.
5. Start the entry queue, if required.

Procedural Notes

Disposal

Dispose of hazardous or biologically contaminated materials according to the practices of your institution. Discard all materials in a safe and acceptable manner, and in compliance with all country and local requirements.

Interpretation of Results

For detailed information about how the system calculates results, refer to the system operating instructions or to the online help system.

The system reports HIV 1/O/2 antibody results in Index Values and as reactive or nonreactive. The minimum level of antibodies to HIV-1/HIV-2 that indicates reactivity is determined based on population studies and is assigned an Index Value of 1.0. This is the Cutoff Index Value.

The Cutoff Index Value of 1.0 is used to determine whether a specimen is reactive or nonreactive for antibodies to HIV-1/HIV-2.

- Specimens with an Index Value of less than 1.0 are considered nonreactive for antibodies to HIV-1 and HIV-2 by the ADVIA Centaur HIV 1/O/2 Enhanced Assay.
- Specimens with an Index Value greater than or equal to 1.0 are considered initially reactive for antibodies to HIV-1 and/or HIV-2 and should be retested in duplicate after centrifugation. If one or both of the duplicates are reactive, the specimen is repeatedly reactive by the ADVIA Centaur HIV 1/O/2 Enhanced Assay.
- Repeatedly reactive specimens must be investigated using supplemental tests for HIV-1 and/or HIV-2. The US Public Health Service may periodically issue recommendations for appropriate use of supplemental tests. In specimens giving indeterminate supplemental test results, testing of a subsequent sample drawn at a later date (such as 1 – 6 months) is recommended. For individuals who are confirmed positive for antibodies, appropriate counseling and medical evaluation should be offered and are considered an important part of testing for antibody to HIV-1 and HIV-2.
- An individual who has antibodies to HIV is presumed to be infected with the virus; however, an individual who has participated in an HIV vaccine study may develop antibodies to the vaccine, and may or may not be infected with HIV. Clinical correlation is indicated with appropriate counseling, medical evaluation, and possibly additional testing

to decide whether a diagnosis of HIV infection is accurate.

- Specimens that are initially reactive are considered negative for HIV-1/HIV-2 antibodies if both of the duplicates retest with an Index Value less than 1.0.
- The cutoff for the ADVIA Centaur HIV 1/O/2 Enhanced assay was verified based on results of Receiver-Operator characteristics (ROC) Curve.[12]

Limitations

- The ADVIA Centaur HIV 1/O/2 Enhanced assay is limited to the detection of antibodies to HIV-1 and/or HIV-2 in human serum or plasma (potassium EDTA, lithium or sodium heparinized, and ACD).
- The calculated values for anti-HIV in a given specimen as determined by assays from different manufacturers can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the assay used. Values obtained with different assay methods cannot be used interchangeably. The reported antibody level cannot be correlated to an endpoint titer.
- The performance of the assay has not been established for populations of infants or children.
- The performance of the ADVIA Centaur HIV 1/O/2 Enhanced assay has not been established with cord blood, neonatal specimens, cadaver specimens, heat-inactivated specimens, or body fluids other than serum or plasma, such as saliva, urine, amniotic or pleural fluids.
- Do not use specimens with obvious microbial contamination.
- It is recognized that currently available assays for the detection of antibodies to HIV-1 and/or HIV-2 may not detect all infected individuals. A negative test result does not exclude the possibility of exposure to or infection with HIV. HIV antibodies may be undetectable in some stages of the infection and in some clinical conditions.

Performance Characteristics

Specificity

The repeatedly reactive rate and diagnostic specificity of the ADVIA Centaur HIV 1/O/2 Enhanced assay was determined using specimens from a population at low risk for HIV-1 or HIV-2 infection.

Specimens were collected from a total of 6060 individuals at low-risk for HIV infection. Of these 6060 specimens, 6011 were collected from healthy (normal) individuals, 24 were obtained from a prenatal population, and 25 from a hospitalized population.

Non-reactive, initially reactive, and repeatedly reactive results for the low-risk populations using the ADVIA Centaur HIV 1/O/2 Enhanced assay are shown below.

	Results Obtained with ADVIA Centaur HIV 1/O/2 Enhanced Assay				*Repeatedly Reactive Specimens*	
Population	*Number Tested*	*Non-Reactive*	*Initially Reactive*	*Repeatedly Reactive*	*HIV-2 Immunoblot Reactive*	*HIV-1 Western blot Reactive*
Healthy	6011	5998	13	7	1	0
Prenatal	24	23	1	1	0	1
Hospitalized	25	25	0	0	0	0
Total	6060	6046 (99.77%)	14 (0.23%)	8 (0.13%)	1 (0.016%)	1 (0.016%)

As shown in the table above, 99.77% (6046/6060) of the low risk population were initially non-reactive, 0.23% (14/6060) were initially reactive, and 0.13% (8/6060) were repeatedly reactive. Of the 8 repeatedly reactive specimens, 1 specimen from the healthy population was positive for antibodies to HIV-2 by immunoblot and 1 from the prenatal population was positive for HIV-1 by Western blot.

The diagnostic specificity of the ADVIA Centaur HIV 1/O/2 Enhanced assay was calculated as follows:

$$\text{Specificity} = \frac{\text{number of specimens in low risk population – number of repeatedly reactive specimens by ADVIA Centaur HIV 1/O/2 Enhanced Assay}}{\text{number specimens in low risk population – number of repeatedly reactive specimens confirmed by immunoblot}} \times 100$$

Of the 6060 specimens tested, 2 were determined to be HIV-1 or HIV-2 positive by confirmatory Western blot and immunoblot testing, respectively. The results from these 2 specimens were excluded from the specificity calculation. The diagnostic specificity of the ADVIA Centaur 1/O/2 Enhanced assay in the low risk population was 99.90% (6052/6058) with a 95% confidence interval of 99.78% to 99.96%.

Sensitivity Studies in Individuals Known to be Positive for Antibodies to HIV-1 and HIV-2

Reactivity and Clinical Sensitivity in Individuals Known to be Positive for Antibodies to HIV-1

The reactivity rate and clinical sensitivity of the ADVIA Centaur HIV 1/O/2 Enhanced assay was assessed in 1059 individuals who were known to be infected with HIV-1. Of the 1059 HIV-1 positive individuals, 251 individuals were symptomatic for AIDS or ARC and 808 individuals were asymptomatic for AIDS or ARC at study enrollment.

The 1059 HIV-1 positive individuals were obtained from the following geographic regions: Florida (221 specimens, 20.87%), Texas (311, 29.37%), New York (455, 42.96%), and Tennessee (72, 6.80%). The reactivity rate of the ADVIA Centaur HIV 1/O/2 Enhanced assay for HIV-1 positive individuals is shown in the table below.

	Results Obtained with ADVIA Centaur HIV 1/O/2 Enhanced Assay				*Licensed HIV-1/HIV-2 EIA*		*Repeatedly Reactive Specimens*
Group	*Number Tested*	*Non-Reactive*	*Initially Reactive*	*Repeatedly Reactive*	*Initially Reactive*	*Repeatedly Reactive*	*HIV-1 Western blot Reactive**
Asymptomatic	808	0	808	808	808	808	808**
Symptomatic	251	0	251	251	251	251	251
Total	1059	0 (0.00%)	1059 (100.0%)	1059 (100.0%)	1059 (100.00%)	1059 (100.00%)	1059 (100.00%)

* Five (5) specimens were found to be immunoblot positive for both HIV-1 and HIV-2.
** One (1) specimen, originally Western blot indeterminate, was subsequently determined to be HIV positive upon additional HIV-1 supplemental testing.

As shown in the table above, 100.00% (1059/1059) of the HIV-1 positive population tested were initially reactive and repeatedly reactive using the ADVIA Centaur HIV 1/O/2 Enhanced assay.

The clinical sensitivity of the ADVIA Centaur HIV 1/O/2 Enhanced assay was 100.00% (1059/1059, 95% CI of 99.72% to 100.00%) in the HIV-1 positive population.

Reactivity in Individuals Known to be Positive for Antibodies to HIV-2

The HIV-2 positive population included 197 individuals who were known to be infected with HIV-2. Specimens from individuals infected with HIV-2 were obtained by commercial vendors from Africa and were sent to the sites for testing. The results of testing are shown in the following table.

Results Obtained with ADVIA Centaur HIV 1/O/2 Enhanced Assay				*Licensed HIV-1/HIV-2 EIA*		*Repeatedly Reactive Specimens*
Number Tested	*Non-Reactive*	*Initially Reactive*	*Repeatedly Reactive*	*Initially Reactive*	*Repeatedly Reactive*	*HIV-2 Immunoblot Reactive**
197	0 (0.00%)	197 (100.00%)	197 (100.00%)	197 (100.00%)	197 (100.00%)	197 (100.00%)

*27 (13.71%) specimens were found to be immunoblot positive for both HIV-1 and HIV-2.

As shown in the table above, 100.00% (197/197) of the HIV-2 positive population tested were initially reactive and repeatedly reactive using the ADVIA Centaur HIV 1/O/2 Enhanced assay.

The clinical sensitivity of the ADVIA Centaur HIV 1/O/2 Enhanced assay was 100.00% (197 of 197 specimens; 95% CI of 98.49% to 100.00%) in the HIV-2 positive population.

Reactivity in Specimens Known to be Positive for Antibodies to HIV-1 Group "O"

Ten specimens from different individuals known to be positive for antibodies to HIV-1 Group "O" were tested with the ADVIA Centaur HIV 1/O/2 Enhanced assay. All ten specimens tested were initially reactive and repeatedly reactive using the ADVIA Centaur HIV 1/O/2 Enhanced assay.

Reactivity in High Risk Populations for HIV-1 and HIV-2

Reactivity in High Risk Populations for HIV-1

Individuals at high risk of HIV-1 infection included 554 prospectively enrolled individuals who had the following risk factors: intravenous drug user (IVDU), transfusion recipient, sexually transmitted diseases, renal dialysis patient, hemophilia, homosexual male and other. The reactivity of specimens from an HIV-1 high risk population is shown below.

Results Obtained with ADVIA Centaur HIV 1/O/2 Enhanced Assay				*Licensed HIV-1/HIV-2 EIA*			*Repeatedly Reactive Specimens*	
Number Tested	*Non-Reactive*	*Initially Reactive*	*Repeatedly Reactive*	*Non-Reactive*	*Initially Reactive*	*Repeatedly Reactive*	*HIV-2 Immunoblot Reactive*	*HIV-1 Western blot Reactive*
554	526 (94.95%)	28 (5.05%)	25 (4.51%)	525 (94.76%)	29 (5.23%)	29 (5.23%)	0 (0.00%)	14 (2.53%)

All 14 specimens confirmed positive by Western blot were repeatedly reactive using the ADVIA Centaur HIV 1/O/2 Enhanced assay (14/14 or 100% detection). Of the 554 specimens tested with the ADVIA Centaur HIV 1/O/2 Enhanced assay, 2.04% (11/540) were repeatedly reactive but not confirmed positive by HIV-1 Western blot. Of the 554 specimens tested with the licensed HIV-1/HIV-2 EIA, 2.78% (15/540) were repeatedly reactive but not confirmed positive by HIV-1 Western blot.

Reactivity in High Risk Populations for HIV-2

Four hundred and eighty-five (485) individuals at high risk for HIV-2 infection were enrolled in this study. These individuals were considered to be at high risk for HIV-2 infection because they resided in an HIV-2 endemic area (Ivory Coast of Africa). All testing of the high-risk HIV-2 population was performed at the Bayer HealthCare site. The reactivity of specimens from an HIV-2 high risk population is shown below.

Results Obtained with ADVIA Centaur HIV 1/O/2 Enhanced Assay				*Licensed HIV-1/HIV-2 EIA*			*Repeatedly Reactive Specimens*	
Number Tested	*Non-Reactive*	*Initially Reactive*	*Repeatedly Reactive*	*Non-Reactive*	*Initially Reactive*	*Repeatedly Reactive*	*HIV-2 Immunoblot Reactive*	*HIV-1 Western blot Reactive*
485	442 (91.13%)	43 (8.86%)	42 (8.66%)	425 (87.63%)	60 (12.37%)	42 (8.66%)	17* (3.50%)	41** (8.45%)

*16 specimens were also HIV-1 Western Blot positive and 1 was HIV-2 only.
** 16 specimens that were HIV-1 Western blot positive were also HIV-2 immunoblot positive.

All 17 specimens confirmed positive by immunoblot were repeatedly reactive using the ADVIA Centaur HIV 1/O/2 Enhanced assay (17/17, 100% detection). All 41 specimens confirmed positive by HIV-1 Western blot were repeatedly reactive using the ADVIA Centaur HIV 1/O/2 Enhanced assay (41/41, 100% detection). All samples that were repeatedly reactive by the ADVIA Centaur HIV 1/O/2 Enhanced assay and the licensed HIV-1 assay were confirmed positive using either or both the HIV-1 Western blot and HIV-2 immunoblot assays.

Seroconversion Studies

Twenty commercially available seroconversion panels were tested using the ADVIA Centaur HIV 1/O/2 Enhanced assay and the reference HIV 1/2 assay.

A summary of seroconversion results is presented in the following table:

ADVIA Centaur HIV 1/O/2 Enhanced Assay
Detection of Antibodies to HIV-1 and/or HIV-2
Seroconversion Panels

Panel ID	*Day of Bleed*[a]	*ADVIA Centaur HIV 1/O/2 Index*	*ADVIA Centaur HIV 1/O/2 Interpretation*[b]	*Reference HIV 1/2 S/CO*	*Reference HIV 1/2 Interpretation*[b]
HIVSCP-001a	42	0.28	NR	0.11	NR
	47	9.59	RR	3.80	RR
PRB916	15	0.2	NR	0.07	NR
	30	23.75	RR	10.95	RR
PRB926	9	0.04	NR	0.07	NR
	27	49.13	RR	>18.18	RR
PRB929	18	0.45	NR	0.08	NR
	21	1.36	RR	0.64	NR
	25	29.32	RR	>18.18	RR
PRB931	15	0.16	NR	0.11	NR
	28	50.01	RR	>18.18	RR
PRB933	0	0.3	NR	0.09	NR
	21	20.91	RR	>18.18	RR
PRB934	0	0.34	NR	0.48	NR
	7	5.49	RR	7.25	RR
PRB935	28	0.56	NR	0.18	NR
	43	14.2	RR	8.91	RR
PRB939 (E)	23	0.11	NR	0.31	NR
	103	43	RR	>16.95	RR
PRB940	7	0.87	NR	0.19	NR
	11	11.72	RR	2.69	RR
PRB941	9	0.04	NR	0.20	NR
	18	4.8	RR	13.52	RR
PRB943	12	0.41	NR	0.16	NR
	14	0.85	NR	1.62	RR
	19	50.01	RR	>16.95	RR
PRB944	7	0.48	NR	0.19	NR
	9	1.19	RR	0.77	NR
	14	40.25	RR	>16.95	RR
PRB945	7	0.04	NR	0.17	NR
	13	4.51	RR	3.38	RR
PRB950	21	0.07	NR	0.12	NR
	28	35.05	RR	>20.18	RR
PRB952	10	0.53	NR	0.17	NR
	14	9.35	RR	0.82	NR
	17	50.01	RR	7.84	RR
PRB957	16	0.53	NR	0.15	NR
	23	10.04	RR	0.94	NR
	28	29.84	RR	13.83	RR
PRB958	9	0.04	NR	0.11	NR
	15	1.87	RR	9.56	RR
PRB959	0	0.25	NR	0.18	NR
	7	1.07	RR	0.69	NR
	9	8.87	RR	3.65	RR

ADVIA Centaur HIV 1/O/2 Enhanced Assay Detection of Antibodies to HIV-1 and/or HIV-2 Seroconversion Panels					
Panel ID	*Day of Bleed*[a]	*ADVIA Centaur HIV 1/O/2 Index*	*ADVIA Centaur HIV 1/O/2 Interpretation*[b]	*Reference HIV 1/2 S/CO*	*Reference HIV 1/2 Interpretation*[b]
RP-002	63	0.31	NR	0.34	NR
	69	2.41	RR	0.57	NR
	71	5.29	RR	2.91	RR

a Day of bleed is the blood draw date minus the date of the first blood draw for the panel. The first draw date is bleed day 0.

b RR = Repeatedly reactive, NR = non-reactive

Compared to the reference assay results, the first time point that was repeatedly reactive in the ADVIA Centaur HIV 1/O/2 Enhanced Assay occurred earlier in 6 panels (2 – 5 days), at the same time in 13 panels, and later in 1 panel (5 days). Overall, compared to the reference HIV assay, the ADVIA Centaur HIV 1/O/2 Enhanced assay demonstrated efficacy for early detection of the appearance of antibodies to HIV following a new HIV infection.

Genotype Study

A group of 65 worldwide specimens known to be infected with subtypes (that is, clades) descended from the HIV-1 group M genotype were sourced from BBI (panel members from WWRB 301, 302, 303), NIBSC (National Institute for Biological Standards and Control), CDC (CDC HIV-1 Groups M and O Cameroonian Blood Bank Panel), and Hospital Carlos in Spain. The specimens were tested in the ADVIA Centaur HIV 1/O/2 Enhanced and reference HIV assays.

Results of testing in the ADVIA Centaur HIV 1/O/2 Enhanced and reference HIV assay for the HIV-1 group M genotype panel are summarized by clade in the following table:

		ADVIA Centaur HIV 1/O/2 Enhanced Result
Clade	*Number of Specimens*	*Number Repeatedly Reactive**
H	1	1
E	2	2
F	1	1
A, E	1	1
A, F	1	1
A, G	4	4
D	1	1
F	1	1
F	2	2
G	2	2
A	6	6
C	7	7
D	5	5
E	3	3
G	3	3
A	1	1
A, C	1	1
A, G	1	1
B, A	1	1
B	4	4
B, C	1	1
B, D	1	1
B, F	1	1
B, F	1	1
C, A	2	2
C	2	2
D, A	1	1
D	2	2
E, A	1	1
E, B	1	1
E, C, A	1	1
E, F, B	1	1
F, B	1	1
F	1	1

* All specimens repeatedly reactive using ADVIA Centaur HIV 1/O/2 Enhanced assay were repeatedly reactive in the Reference HIV 1/2 assay.

Samples from 65 specimens (100.00%) in the HIV-1 group M genotype panel were reactive in the ADVIA Centaur HIV 1/O/2 Enhanced and reference HIV assays. The following clades from the HIV-1 group M genotype were detected: A, B, C, D, E, F, G, and H.

The ADVIA Centaur HIV 1/O/2 Enhanced and reference assays detected HIV infection in samples from 10 of 10 patients (100%) who were infected with the HIV-1 group O genotype.

System Reproducibility

The precision of the ADVIA Centaur HIV 1/O/2 Enhanced assay was tested at 3 testing sites using a 12-member panel and 3 reagent lots. The 12-member panel included 5 dilutions of a sample containing antibodies to HIV-1, 5 dilutions of a sample containing antibodies to HIV-2, and 2 undiluted HIV nonreactive samples. Also tested were positive controls for HIV-1, HIV-1 group O, and HIV-2; and a negative control for HIV-1/O/2. The 12-member panel and controls were assayed in replicates of 5 on a single run per day over 6 days for each lot. The study was completed with a single calibration of the assay (one calibration interval).

The data from all 3 sites and from all 3 reagent lots were combined to achieve SD and percent CV for within run, between run, between testing site, between lot, and total. The precision estimates were derived from variance component analysis. The reproducibility results are presented in the following table:

System Reproducibility for All Testing Sites and Reagent Lots

ADVIA Centaur HIV 1/O/2 Enhanced Assay
System Reproducibility
All Testing Sites and Reagent Lots

Panel Member	Mean ADVIA Centaur HIV Index Value	Within Run[a]		Between Run[b]		Between Testing Site[c]		Between Lot[d]		Total[e]		Number of Observations
		SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	
HIV-1 high negative	0.94	0.081	8.60	0.050	5.32	0.081	8.64	0.029	3.09	0.128	13.65	270
HIV-1 low positive	5.07	0.218	4.30	0.213	4.20	0.290	5.73	0.067	1.32	0.426	8.40	270
HIV-1 high positive	12.06	0.474	3.93	0.582	4.83	0.799	6.63	0.439	3.64	1.181	9.80	270
HIV-2 high negative	0.89	0.129	14.46	0.116	12.99	0.064	7.21	0.044	4.91	0.190	21.30	267*
HIV-2 low positive	5.20	0.267	5.13	0.173	3.33	0.234	4.50	0.285	5.48	0.487	9.37	269*
HIV-2 high positive	12.07	0.471	3.90	0.485	4.02	0.822	6.81	0.669	5.55	1.257	10.42	270
Negative	0.29	0.071	NA	0.039	NA	0.072	NA	0.084	NA	0.138	NA	270
HIV-1 Group “O” low positive	4.52	0.377	8.35	0.190	4.20	0.255	5.64	0.918	20.31	1.042	23.06	270
HIV-1 Group “O” high positive	11.04	0.981	8.88	0.434	3.93	0.731	6.62	2.173	19.69	2.531	22.93	270
HIV-1 high positive	18.54	0.805	4.34	0.918	4.95	1.405	7.58	0.322	1.74	1.889	10.19	270
HIV-2 high positive	18.40	0.806	4.38	0.921	5.01	1.525	8.29	0.997	5.41	2.195	11.93	270
Negative	0.29	0.080	NA	0.047	NA	0.075	NA	0.095	NA	0.153	NA	270
HIV-1/O/2 Negative Control	0.22	0.053	NA	0.049	NA	0.089	NA	0.084	NA	0.142	NA	265*
HIV-1 Positive Control	3.20	0.143	4.47	0.080	2.50	0.135	4.22	0.041	1.29	0.216	6.76	270
HIV-2 Positive Control	5.62	0.250	4.44	0.201	3.58	0.232	4.12	1.255	22.31	1.316	23.39	270
HIV-1 Group “O” Positive Control	3.61	0.263	7.27	0.125	3.47	0.078	2.17	0.204	5.64	0.364	10.07	270

NA = Not applicable

Note: 5 replicates per panel in 1 run per day for 6 days

a Variability of the assay performance within day (all testing sites and reagent lots).

b Variability of the assay performance between days (all testing sites and reagent lots).

c Variability of the assay performance between testing sites (from testing site to testing site).

d Variability of the assay performance between reagent lots (from reagent lot to reagent lot, across all testing sites).

e Variability of the assay performance incorporating all testing sites, all reagent lots, and all days.

* Outliers, defined as values outside the range of 5.5 SD per panel member were not included in this analysis. Outliers were identified for HIV-2 high negative panel (3 replicates), HIV-2 low positive panel (1 replicate), and the HIV-1/O/2 negative control (2 replicates) in the calculation of precision and reproducibility estimates for one lot at one testing site.

Cross-Reactivity

The ADVIA Centaur HIV 1/O/2 Enhanced assay was evaluated for potential cross-reactivity with other viral infections and disease state specimens. Specimens were obtained from the following vendors: ProMedDx LLC, Norton, MA; Teragenix, Ft. Lauderdale, FL; Profile Diagnostics, Sherman Oaks, CA; and SeraCare, Oceanside, CA. The reactive HIV status of each specimen was verified using an anti-HIV reference assay. The following results were obtained using the ADVIA Centaur HIV 1/O/2 Enhanced assay:

		Number of Reactive Anti-HIV Results	
Clinical Category	*Number Tested*	*ADVIA Centaur Assay*	*Reference Assay*
Hepatitis A Infection (HAV)	10	0	0
Hepatitis B Infection (HBV)	10	0	0
Hepatitis C Infection (HCV)	10	0	0
Epstein-Barr Virus (EBV) IgG	10	0	0
Epstein-Barr Virus (EBV) IgM	10	0	0
Herpes Simplex Virus (HSV) IgG	10	0	0
Herpes Simplex Virus (HSV) IgM	10	0	0
Syphilis IgG	10	0	0
Syphilis IgM	10	0	0
Varicella Zoster (VZV) IgG	10	0	0
Cytomegalovirus (CMV) IgG	10	0	0
Cytomegalovirus (CMV) IgM	3	0	0
Rubella IgG	10	0	0
Toxoplasma IgG	10	0	0
Toxoplasma IgM	10	0	0
Human T-cell Lymphotropic Virus (HTLV I/II)	10	0	0
Alcoholic Hepatitis	2	0	0
Multiparity	10	0	0
Flu Vaccine Recipient	10	4*	4*
Rheumatoid Arthritis (RF)	10	0	0
Anti-Nuclear Antibody (ANA)	10	0	0
Human Anti-Mouse Antibody (HAMA)	10	0	0
Crohn's Disease	10	0	0
Mixed Connective Tissue Disease (MCTD)	10	0	0
Systemic Lupus Erythematosus (SLE)	10	0	0
Ulcerative colitis	10	0	0
Elevated IgA	3	0	0
Elevated IgM	2	0	0
Elevated IgG	5	0	0
Graves' Disease	7	0	0
Vasculitis	10	0	0
Fibromyalgia	10	0	0
Scleroderma	10	0	0
Total Sample Tested	292	4	4

*Four flu vaccine recipient specimens reactive by ADVIA Centaur HIV 1/O/2 Enhanced assay were also reactive by the Reference assay and by HIV-1 Western blot.

Endogenous Interferents

The ADVIA Centaur HIV 1/O/2 Enhanced assay was evaluated for interference according to CLSI Document EP7-A2.[13] None of the interferents at the levels tested produced a change in clinical interpretation of the assay. In addition, a potentially interfering effect of biotin was evaluated using the four control sample spiked with several levels of biotin. No interference was observed. An evaluation with cholesterol was performed with 10 samples in both serum and potassium EDTA plasma at 2 levels. No interference was observed.

Serum specimens that are . . .	*Demonstrate no clinically significant difference up to . . .*
hemolyzed	500 mg/dL of hemoglobin
lipemic	3000 mg/dL of triglycerides
icteric[1]	60 mg/dL of conjugated bilirubin
icteric	40 mg/dL of unconjugated bilirubin
proteinemic[2]	3.5 g/dL of protein
high protein	12 g/dL
hyper-IgG	12 g/dL of immunoglobulin G
biotin	500 ng/mL
cholesterol	500 mg/dL

1 Serum and EDTA plasma samples positive for antibodies to HIV and spiked with high levels of conjugated bilirubin showed an increase in signal of up to 27% at 30 mg/dL and 36% at 60 mg/dL compared to unspiked controls. This effect was not observed with heparin or ACD plasma samples. There is no effect on negative specimens in any tube type. The effect of spiked conjugated bilirubin had no impact on clinical interpretation of any sample.

2 Serum, ACD, Li Heparin, Na Heparin, and K2EDTA specimens diluted with buffer to < 3.5 mg/dL protein and spiked with antibody to HIV-1, HIV-2 or HIV-1 group O showed reduced signals up to 36% compared with spiked normal controls. Based on the results of the contrived low protein samples, high negative specimens with abnormally low protein levels should be considered for follow-up testing.

Standardization

The ADVIA Centaur HIV 1/O/2 Enhanced assay standardization is based upon relative clinical agreement with commercially available anti-HIV assays. Assigned values for calibrators and controls are traceable to this standardization.

Technical Assistance

For customer support, please contact your local technical support provider or distributor.

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