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Evaluation of the Analytical Performance of the Herpes Simplex Virus Type 1 and Type 2 IgG Assays on the Atellica CI Analyzer

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Background

Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are highly prevalent pathogens, mainly sexually transmitted, that usually remain latent and asymptomatic in immunocompetent individuals. HSV-1 most often causes oral lesions, whereas HSV-2 is associated with genital lesions. HSV-2 is also the leading cause of neonatal herpes infection, which is usually acquired during delivery when active maternal infection is present, particularly in non-immune pregnant women.[1]

Type-specific HSV-1 and HSV-2 IgG serological assays are reliable antibody tests used to detect IgG directed against HSV-1 and HSV-2 in serum. These assays are designed to differentiate between HSV-1 and HSV-2 infections, despite the potential for cross-reactivity between the two viruses. They are valuable for diagnosing infection, characterizing prior exposure, and guiding patient counseling and antiviral treatment decisions, especially in efforts to prevent neonatal HSV-2 infection. Accordingly, HSV testing as part of the ToRCH panel is recommended for pregnant women at risk of HSV infection, particularly those with no history of genital herpes but with a sexual partner known to have HSV infection.[2]

Among the available HSV serological assays, the Atellica IM Herpes-1 IgG (HSV1) and Herpes-2 IgG (HSV2) assays were previously developed and commercialized for use on the Atellica IM Analyzer.[3,4] Recently, the Atellica CI Analyzer (Figure 1) was added to the Atellica Solution portfolio, with a reduced footprint of 1.9 square meters. The Atellica CI Analyzer is an integrated clinical chemistry and immunoassay analyzer designed for low- to mid-volume laboratories and features the same reagents, consumables, and sophisticated user interface as the Atellica IM Analyzer.[5]



Figure 1. The Atellica CI Analyzer

To evaluate the analytical performance of the Atellica IM HSV 1 and HSV2 assays using the Atellica CI analyzer, precision and method comparison (MC) were assessed as performance indicators.

Material and Methods

Precision (CLSI EP05-A3)

Repeatability and Within-Laboratory Precision

- Sample types: native and contrived human serum pools spiked with individual human HSV-1 or HSV-2 positive serum samples, and quality control (QC) samples.
- One aliquot/sample; tested in duplicate; two runs/day ≥2 hours apart for 20 days.
- One reagent lot; two analyzers; total n=80 replicates for each system/lot combination.
- One representative system/lot combination result across all lot and system combinations tested is shown (Tables 1 & 3).
- Each testing day, new frozen sample aliquots were thawed and tested. Calibrators and QC materials were handled according to the manufacturer's instructions; two calibration events were incorporated in the 20-day-precision study.

Reproducibility

- n=5 replicates/sample; one run/day for five days; three reagent lots, three analyzers; total n=225 measurements per sample.
- Data were analyzed using a balanced crossed and nested ANOVA design where the factors Instrument and Reagent Lot are crossed, Day is nested within both Instrument and Reagent Lot, and Replicate is nested within Day. The following variance components were estimated for each sample: repeatability, between-day, between-lot, and between-instrument. Reproducibility (total imprecision) was computed as the root sum of squares of all variance components estimates.

Method comparison (CLSI EP12-A2)

- MC was evaluated using individual native serum samples stored frozen in aliquots at ≤-20°C. Samples were thawed and centrifuged before tested on the Atellica CI Analyzer, the ADVIA Centaur XP system, and the Atellica IM Analyzer using three reagent lots.
- Samples (n ~ 230) were acquired from Siemens Healthineers approved vendors from HSV positive individuals and negative individuals.
- MC was completed over 5 nonconsecutive days using a single calibration event.
- One representative system/lot combination result across all lot and system combinations tested is presented (Tables 5,6,7 & 8).
- One replicate was processed per sample.
- A separate MC study was conducted for each assay using the ACCUSET HSV-1/2 mixed titer performance panel PTH202 (Seracare) consisting of a set of 21 naturally occurring members with reactivity ranging from negative to strongly positive for anti-HSV 1/2 IgG and IgM markers.
- Samples were classified, using 1.00 Index cutoff, as reactive (Index ≥1.00) or nonreactive (Index <1.00) specimens for the presence of antibodies to HSV-1 or HSV-2.
- Relative sensitivity, relative specificity, and overall agreement are reported and were calculated as follows:

		Atellica IM (or ADVIA Centaur XP) Result	
		Reactive	Nonreactive
Atellica CI Result	Reactive	A	B
	Nonreactive	C	D

Relative sensitivity = 100 × A / (A + C)
Relative specificity = 100 × D / (B + D)
Overall Percent Agreement = 100 × (A + D) / (A + B + C + D)

Results

Precision

Table 1. Precision for the Atellica IM HSV1 assay on the Atellica CI Analyzer

Specimen Type	Mean (n=80) (Index)	Repeatability		Within-laboratory Precision	
		SD (Index)	CV (%)	SD (Index)	CV (%)
Serum A[a]	0.02	0.022	N/A	0.028	N/A
Serum B	0.62	0.013	2.1	0.050	8.1
Serum C	0.91	0.013	1.4	0.034	3.7
Serum D	2.18	0.032	1.5	0.081	3.7
Serum E	4.96	0.068	1.4	0.187	3.8
Serum F	8.72	0.124	1.4	0.305	3.5
QC 1	0.21	0.009	N/A	0.025	N/A
QC 2	2.97	0.049	1.6	0.129	4.3

CV, coefficient of variation; N/A, not applicable. The results remained nonreactive throughout the study; SD, standard deviation.
[a]n=78 numeric index data included in the analysis for this sample while two replicates resulting below assay reportable range were excluded.

The Atellica IM HSV1 assay on the Atellica CI Analyzer demonstrated ≤2.1% repeatability CV and ≤8.1% within-laboratory precision CV across the sample interval tested (0.62–8.72 Index).

Table 2. Reproducibility for the Atellica IM HSV1 assay on the Atellica CI Analyzer

Sample	Mean (n=225) (Index)	Repeat-ability		Between-DAY		Between-LOT		Between-INSTRUMENT		Repro-ducibility	
		SD (Index)	CV (%)	SD (Index)	CV (%)	SD (Index)	CV (%)	SD (Index)	CV (%)	SD (Index)	CV (%)
Serum A	0.01	0.003	N/A	0.009	N/A	0.002	N/A	0.009	N/A	0.013	N/A
Serum B	0.53	0.009	1.7	0.020	3.8	0.050	9.4	0.023	4.3	0.059	11.1
Serum C	0.89	0.027	3.0	0.010	1.1	0.017	1.9	0.033	3.7	0.047	5.3
Serum D	2.14	0.128	6.0	0.019	0.9	0.063	2.9	0.082	3.8	0.165	7.7
Serum E	5.06	0.108	2.1	0.080	1.6	0.322	6.4	0.185	3.7	0.395	7.8
Serum F	8.35	0.198	2.4	0.132	1.6	0.154	1.8	0.308	3.7	0.419	5.0
QC 1	0.25	0.007	N/A	0.014	N/A	0.034	N/A	0.017	N/A	0.041	N/A
QC 2	2.96	0.040	1.4	0.060	2.0	0.069	2.3	0.083	2.8	0.130	4.4

N/A, not applicable. The results remained nonreactive throughout the study

Across the sample interval tested, HSV1 reproducibility was ≤11.1%.

Table 3. Precision for the Atellica IM HSV2 assay on the Atellica CI Analyzer

Specimen Type	Mean (n=80) (Index)	Repeatability		Within-laboratory Precision	
		SD (Index)	CV (%)	SD (Index)	CV (%)
Serum A	0.16	0.004	N/A	0.011	N/A
Serum B	0.67	0.009	1.3	0.028	4.2
Serum C	0.92	0.011	1.2	0.036	3.9
Serum D	2.04	0.027	1.3	0.074	3.6
Serum E	5.18	0.067	1.3	0.215	4.2
Serum F	9.49	0.102	1.1	0.353	3.7
QC 1	0.28	0.006	N/A	0.015	N/A
QC 2	3.12	0.045	1.4	0.155	5.0

N/A, not applicable. The results remained nonreactive throughout the study.

The Atellica IM HSV2 assay on the Atellica CI Analyzer demonstrated ≤1.4% repeatability CV and ≤5.0% within-laboratory precision CV across the sample interval tested (0.67–9.49 Index).

Table 4. Reproducibility for the Atellica IM HSV2 assay on the Atellica CI Analyzer

Sample	Mean (n=225) (Index)	Repeat-ability		Between-DAY		Between-LOT		Between-INSTRUMENT		Repro-ducibility	
		SD (Index)	CV (%)	SD (Index)	CV (%)	SD (Index)	CV (%)	SD (Index)	CV (%)	SD (Index)	CV (%)
Serum A	0.17	0.005	NA	0.006	NA	0.016	NA	0.000	NA	0.017	NA
Serum B	0.67	0.066	9.9	0.011	1.6	0.037	5.5	0.002	0.3	0.077	11.5
Serum C	0.88	0.015	1.7	0.017	1.9	0.012	1.4	0.007	0.8	0.027	3.1
Serum D	1.90	0.073	3.8	0.039	2.1	0.015	0.8	0.000	0.0	0.084	4.4
Serum E	4.94	0.090	1.8	0.117	2.4	0.019	0.4	0.021	0.4	0.150	3.0
Serum F	9.07	0.147	1.6	0.411	4.5	0.064	0.7	0.158	1.7	0.468	5.2
QC 1	0.29	0.008	NA	0.008	NA	0.011	NA	0.004	NA	0.016	NA
QC 2	3.03	0.052	1.7	0.080	2.6	0.000	0.0	0.008	0.3	0.095	3.1

N/A, not applicable. The results remained nonreactive throughout the study

Across the sample interval tested, HSV2 reproducibility was ≤11.5%..

Method Comparison

Table 5. Qualitative method comparison for the Atellica IM HSV1 assay on the Atellica IM and Atellica CI Analyzers

1.00 Index Cutoff		Atellica IM HSV1 on the Atellica IM Analyzer		
		Reactive	Nonreactive	Total
Atellica IM HSV1 on the Atellica CI Analyzer	Reactive	135	0	135
	Nonreactive	0	103	103
	Total	135	103	238

Relative sensitivity: 100% (135/135); 95% confidence interval: 97.23–100%

Relative specificity: 100% (103/103); 95% confidence interval: 96.41–100%

Table 6. Qualitative method comparison for the Atellica IM HSV1 assay on the Atellica CI Analyzer and ADVIA Centaur XP system

1.00 Index Cutoff		ADVIA Centaur HSV1 on the ADVIA Centaur XP system		
		Reactive	Nonreactive	Total
Atellica IM HSV1 on the Atellica CI Analyzer	Reactive	135	0	135
	Nonreactive	0	103	103
	Total	135	103	238

Relative sensitivity: 100% (135/135); 95% confidence interval: 97.23–100%

Relative specificity: 100% (103/103); 95% confidence interval: 96.41–100%

The design requirements for method comparison were met with a 100% relative specificity and 100% relative sensitivity when comparing the Atellica IM HSV1 assay using the Atellica CI Analyzer to the Atellica IM Analyzer, as well as to the ADVIA Centaur HSV1 assay using the ADVIA Centaur XP system. No discordant results were observed.

A 100% total agreement was observed between the three compared analyzers (Atellica CI, Atellica IM and ADVIA Centaur XP) for the commercial panel PTH202 using the HSV1 assay.

Table 7. Qualitative method comparison for the Atellica IM HSV2 assay on the Atellica IM and Atellica CI Analyzers

1.00 Index Cutoff		Atellica IM HSV2 on the Atellica IM Analyzer		
		Reactive	Nonreactive	Total
Atellica IM HSV2 on the Atellica CI Analyzer	Reactive	106	0	106
	Nonreactive	2	116	118
	Total	108	116	224

Relative sensitivity: 98.1% (106/108); 95% confidence interval: 93.50–99.49%

Relative specificity: 100% (116/116); 95% confidence interval: 96.80–100%

The two discordant samples were samples, within 15% of the 1.00 Index cutoff value using the Atellica IM HSV2 assay. First replicate results used for relative sensitivity calculation were as follows: Atellica IM/Atellica CI Index values, 1.02/0.85 and 1.03/0.99. Additional replicates during investigation showed concordance for these samples after repeat testing.

Table 8. Qualitative method comparison for the Atellica IM HSV2 assay on the Atellica CI Analyzer and ADVIA Centaur XP system

1.00 Index Cutoff		ADVIA Centaur HSV2 on the ADVIA Centaur XP system		
		Reactive	Nonreactive	Total
Atellica IM HSV2 on the Atellica CI Analyzer	Reactive	106	1	107
	Nonreactive	0	117	117
	Total	106	118	224

Relative sensitivity: 100% (106/106); 95% confidence interval: 96.50–100%

Relative specificity: 99.2% (117/118); 95% confidence interval: 95.36–99.85%

The single discordant sample was within ~15% of the 1.00 Index cutoff value using the Atellica IM and ADVIA Centaur HSV2 assay (ADVIA Centaur/Atellica CI initial Index values, 0.97/1.18). Duplicate retesting during the investigation showed that the sample remained discordant, with replicate Index values fluctuating around the cutoff (0.98, 1.01, 1.02, 1.15, and 1.18) across three reagent lots on Atellica CI. Repeat testing on ADVIA Centaur XP, limited to a single reagent lot because of reagent availability, yielded Index values of 1.00 and 0.99.

The design requirements for method comparison were met with >99% relative specificity and >98% relative sensitivity when comparing the Atellica IM HSV2 assay using the Atellica CI Analyzer to the Atellica IM Analyzer, as well as to the ADVIA Centaur HSV2 assay using the ADVIA Centaur XP system.

A 100% total agreement was observed between the three compared analyzers (Atellica CI, Atellica IM and ADVIA Centaur XP) for the commercial panel PTH202 using the HSV2 assay.

Conclusion

All results indicate that the Atellica IM HSV1 and HSV2 assays on the Atellica CI Analyzer demonstrated good precision and performance capability comparable to the same assays on the Atellica IM Analyzer.

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