Performance Evaluation of Two Recently FDA-approved Ag/Ab Combo Assays in Early HIV-1 infections

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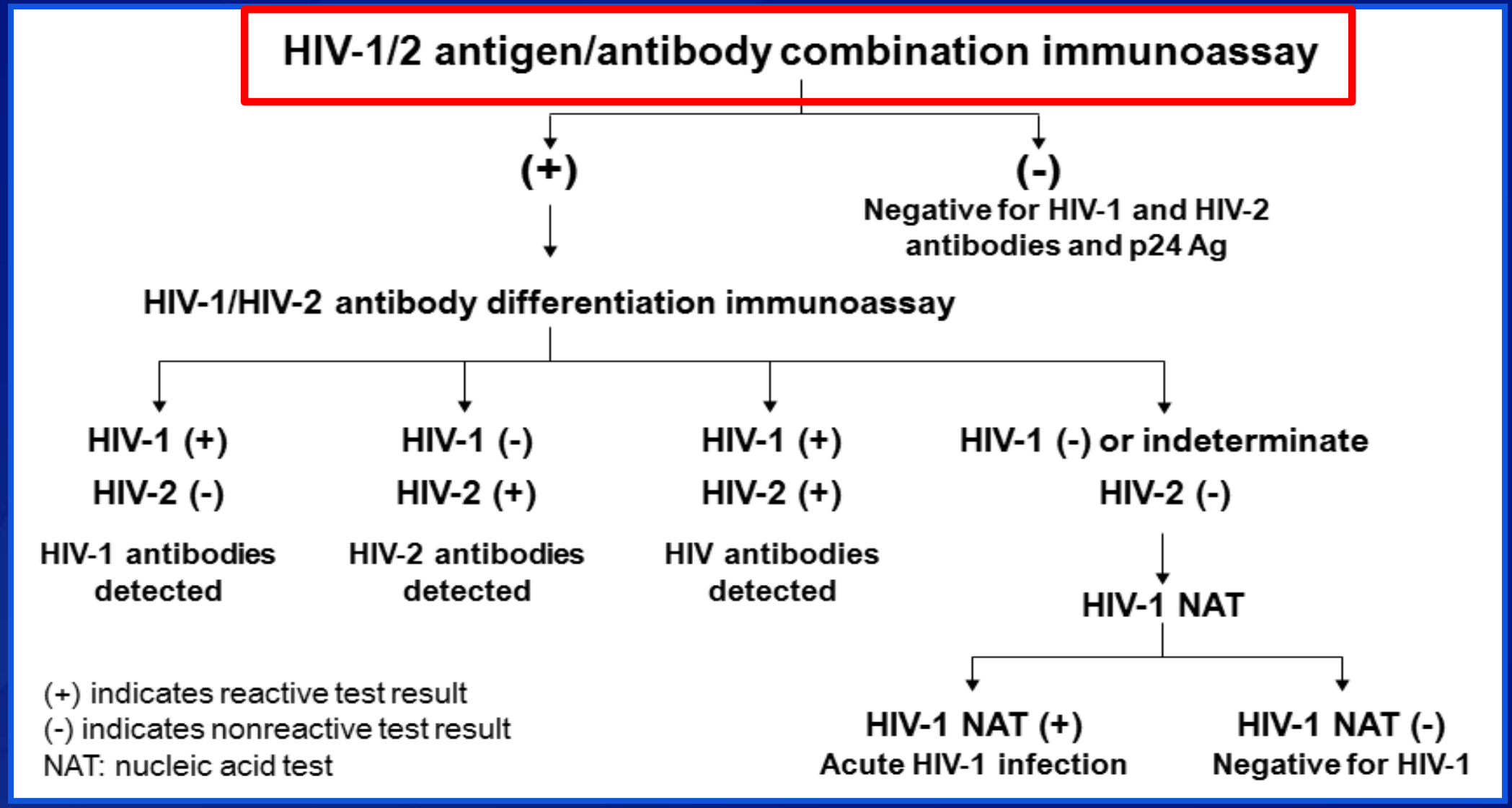
Background

- On going development and FDA approval of improved diagnostic technology
- FDA approved two HIV antigen/antibody combo assays
- Performance evaluation of new technology in the CDC/APHL HIV diagnostic algorithm in laboratory setting is needed to keep the recommendations updated

CDC HIV guidelines for HIV diagnostics in laboratory setting



Objective

- To evaluate the performance of the recently FDA-approved Ag/Ab combo assays

Recently FDA-approved assays

- ADVIA Centaur HIV Ag/Ab Combo (CHIV) Assay

Device Generic Name: Human Immunodeficiency Virus (HIV) p24 antigen and antibodies to HIV Type 1 (HIV-1 group M and group O) and/or Type 2

Manufacturer: Siemens Healthcare Diagnostics, Inc.

Approval Date: June 8, 2015

- Chemiluminescent microparticle immunoassay
- Simultaneous qualitative detection of p24 antigen and antibodies to HIV-1 (groups M and O) and HIV-2 in serum using the ADVIA Centaur and ADVIA Centaur XP systems (high throughput testing)
- The ADVIA Centaur CHIV assay is intended to be used as an aid in the diagnosis of HIV infection in pediatric and adult populations, including pregnant women

Recently FDA-approved assays

- BioPlex®2200 HIV Ag-Ab Assay (BioPlex-C)

Device Generic Name: Human Immunodeficiency Virus (HIV) p24 antigen and antibodies to HIV Type 1 (HIV-1 group M and group O) and/or Type 2

Manufacturer: Bio-Rad Laboratories

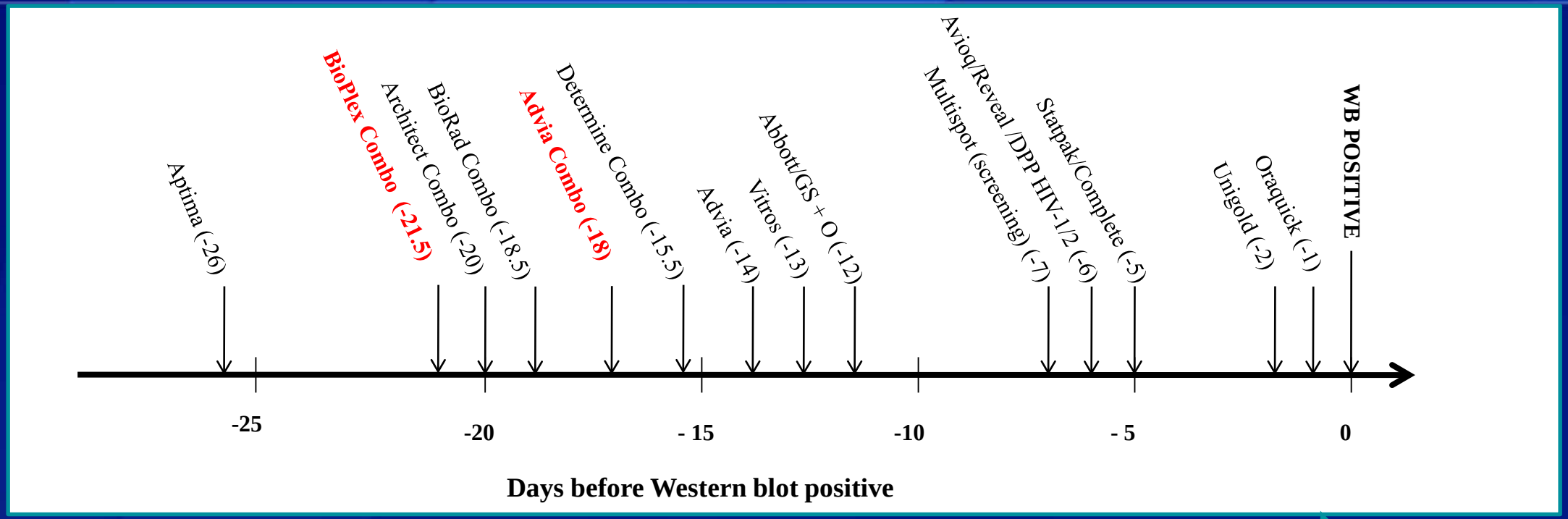
Approval Date: July 23, 2015

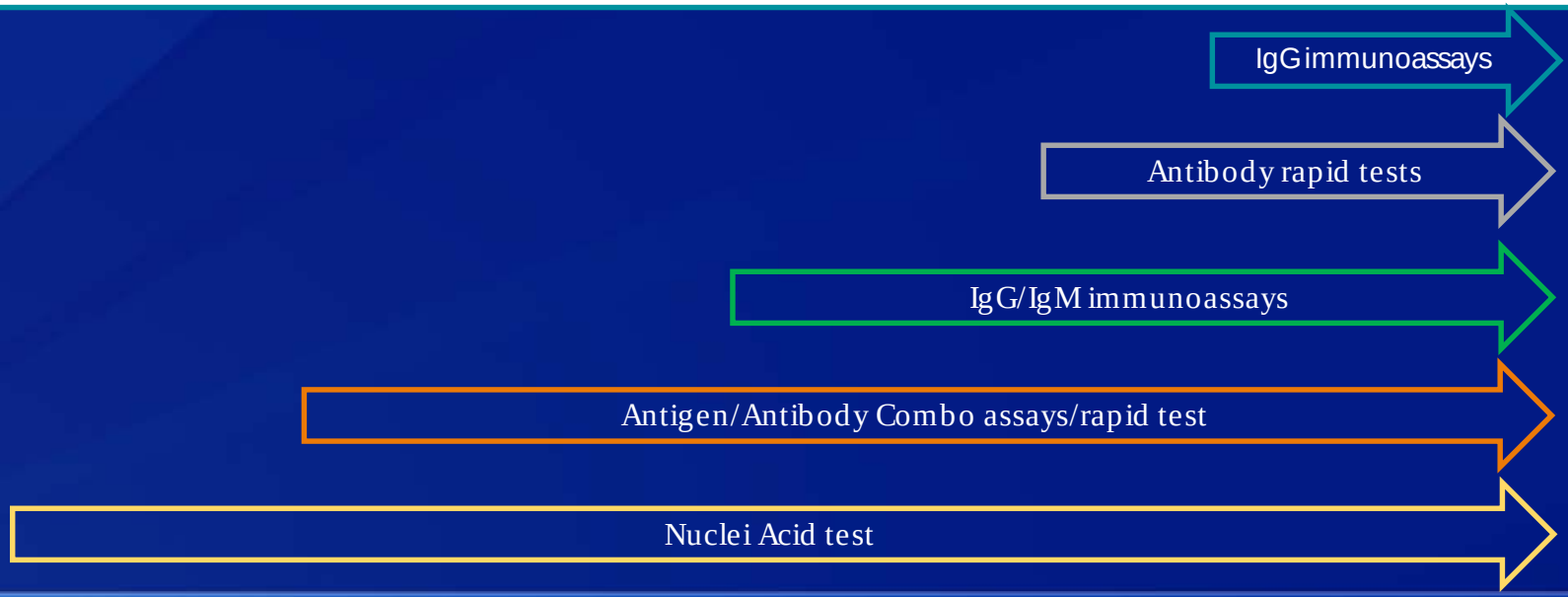
- Multiplex flow immunoassay
- Simultaneous qualitative detection and differentiation of the individual analytes HIV-1 p24 antigen, HIV-1 (groups M and O) antibodies, and HIV-2 antibodies in human serum or plasma (high throughput testing)
- Intended as an aid in the diagnosis of infection with HIV-1 and/or HIV-2, including acute (primary) HIV-1 infection. The assay may also be used as an aid in the diagnosis of infection with HIV-1 and/or HIV-2 in pediatric subjects (≥2 years old), and pregnant women

Sample sets and analysis

- **Plasma specimens from previously characterized commercial seroconverters from the US**
  - BioPlex-C at CDC during clinical trial
  - CHIV at Siemens
- **Assay performance was evaluated**
  - 50% cumulative frequency analysis
    - 17 seroconverters with HIV-1 WB positive
  - Paired comparison with McNemar's tests to previously generated data with Ag/Ab Combo tests approved in the USA
    - 26 seroconverters
  - Ag detection was compared to Roche HIV-1 RNA viral load results

Results


Aptima (-26)
BioPlex Combo (-21.5)
Architect Combo (-20)
BioRad Combo (-18.5)
Advia Combo (-18)
Determine Combo (-15.5)
Advia (-14)
Vitros (-13)
Abbott/GS + O (-12)
Avioq/Reveal /DPP HIV-1/2 (-6)
Multispot (screening) (-7)
Statpak/Complete (-5)
Unigold (-2)
Oraquick (-1)
WB POSITIVE
-25
-20
- 15
-10
- 5
0
Days before Western blot positive


IgG immunoassays
Antibody rapid tests
IgG/IgM immunoassays
Antigen/Antibody Combo assays/rapid test
Nuclei Acid test

Paired comparison analysis in 26 seroconverters

	Results reference test/CHIV				
	NR/NR	NR/R	R/NR	R/R	*p value*
Reference tests					
Determine Combo	95	5	1	121	*0.2207*
Bio-Rad HIV Ag-Ab Combo	86	10	10	116	*0.8231*
Architect HIV Ag-Ab Combo	85	6	11	120	*0.332*

	Results reference test/BioPlex-C				
	NR/NR	NR/R	R/NR	R/R	*p value*
Reference tests					
Determine Combo	90	13	1	125	*0.0033**
Bio-Rad HIV Ag-Ab Combo	90	8	1	130	*0.0455**
Architect HIV Ag-Ab Combo	88	5	3	133	*0.7237*

* Significant difference; NR: non-reactive; R: reactive

Ag/Ab Combo assays and second negative window

Vendor ID	collection date	**Roche V2.0 Viral load** cop/ml	BioPlex-C **Ag**	BioPlex-C **Ab**	ARCH **Ag-Ab**	Combo **Ag-Ab**	CHIV **Ag-Ab**	DC **Ag**	DC **Ab**
9012-01	11/12/1997	1.75×10^5	R	R	R	R	R	NR	NR
9012-02	11/14/1997	TND	NR	NR	NR	NR	NR	NR	NR
9012-03	11/19/1997	$< 2 \times 10^1$ (BRD)	NR	NR	NR	NR	NR	NR	NR
9012-04	11/21/1997	1.02×10^2	NR	NR	NR	NR	n/a	NR	NR
9012-05	11/26/1997	3.61×10^4	R	NR	NR	NR	n/a	NR	NR
9012-06	11/28/1997	8.99×10^4	R	NR	R	R	n/a	R	NR
9014-01	11/13/1997	2.90×10^4	R	NR	R	NR	NR	NR	NR
9014-02	11/15/1997	7.13×10^3	NR	NR	NR	NR	NR	NR	NR
9014-03	11/23/1997	2.20×10^2	NR	R	R	R	R	NR	R
9032-07	7/28/1998	4.49×10^4	R	NR	NR	NR	NR	NR	NR
9032-08	7/30/1998	2.76×10^4	R	NR	R	NR	R	R	NR
9032-09	8/4/1998	2.81×10^4	NR	NR	R	NR	R	NR	R
9032-10	8/11/1998	3.72×10^3	NR	R	R	R	R	NR	R

- BioPlex-C showed a second negative phase during seroconversion

Antigen reactivity with BioPlex-C

BioPlex-C			viral load copies/ml	
Ag	Ab	n	**mean**	**range**
neg	neg	32	7.3 x10^3	TND- 1.39x10^5
pos	neg	42	1.07x10^6	85.8- >10^7
pos	**pos**	41	1.53x10^6	TND- >10^7
neg	**pos**	56	1.26x10^5	TND- 3.54x10^6

- The BioPlex 2200 System output for the HIV-1 p24 Ag results will be "Not reportable due to high HIV Ab level" (without Indices) when HIV-1 and/or HIV-2 antibody levels are very high the antibody may interfere with HIV-1 p24 Ag results
- Samples considered after the first HIV-1 RNA positive
- Ag was detected in samples that had undetectable VL

Summary

- BioPlex-C performed similarly to Architect, but significantly better than GS-Combo and DC
- CHIV performed similarly to GS-Combo, DC and Architect
- BioPlex-C and CHIV were reactive 21.5 and 18 days, respectively, before the first WB-positive
- BioPlex-C can distinguish Ag-reactivity, but no correlation with the viral load was observed
- BioPlex-C exhibits a second negative window

Conclusions

- Recently FDA-approved Ag/Ab Combo assays perform well and detect infection earlier than Ab-only assays
- The cumulative frequency analysis allows a relative comparison of assays' performance using the same sample set and it does not provide an exact value
- Like the rapid test DC, BioPlex-C allows identification of Ag-reactive specimens, but BioPlex-C detected Ag sooner than DC in plasma specimens

Conclusions II

- Use of an Ag/Ab differentiation in the first step of the algorithm may lead to a revision of the current recommended laboratory algorithm
- Studies are needed to document the public health and individual benefits of Ag only detection as a first step in the algorithm

Acknowledgements

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Thank you!

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