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

Silvina Masciotra
Special Studies and Training Activity Lead
HIV Incidence and Diagnostics Team

2016 HIV Diagnostics Conference
Atlanta, March 22, 2016
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

HIV-1/2 antigen/antibody combination immunoassay

(+)

(-)

Negative for HIV-1 and HIV-2 antibodies and p24 Ag

HIV-1/HIV-2 antibody differentiation immunoassay

HIV-1 (+)  HIV-1 (-)  HIV-1 (+)  HIV-1 (-) or indeterminate
HIV-2 (-)  HIV-2 (+)  HIV-2 (+)  HIV-2 (-)

HIV-1 antibodies detected  HIV-2 antibodies detected  HIV antibodies detected  HIV-1 NAT

(+), HIV-1 NAT (+)  (-), HIV-1 NAT (-)

Acute HIV-1 infection  Negative for HIV-1

(+), indicates reactive test result
(-), indicates nonreactive test result
NAT: nucleic acid test
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
Days before Western blot positive

-25
-20
-15
-10
-5
0

WB POSITIVE

IgG immunoassays

Antibody rapid tests

IgG/IgM immunoassays

Antigen/Antibody Combo assays/rapid test

Nucleic Acid test
Paired comparison analysis in 26 seroconverters

### Results reference test/CHIV

<table>
<thead>
<tr>
<th>Reference tests</th>
<th>NR/NR</th>
<th>NR/R</th>
<th>R/NR</th>
<th>R/R</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine Combo</td>
<td>95</td>
<td>5</td>
<td>1</td>
<td>121</td>
<td>0.2207</td>
</tr>
<tr>
<td>Bio-Rad HIV Ag-Ab Combo</td>
<td>86</td>
<td>10</td>
<td>10</td>
<td>116</td>
<td>0.8231</td>
</tr>
<tr>
<td>Architect HIV Ag-Ab Combo</td>
<td>85</td>
<td>6</td>
<td>11</td>
<td>120</td>
<td>0.332</td>
</tr>
</tbody>
</table>

### Results reference test/BioPlex-C

<table>
<thead>
<tr>
<th>Reference tests</th>
<th>NR/NR</th>
<th>NR/R</th>
<th>R/NR</th>
<th>R/R</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine Combo</td>
<td>90</td>
<td>13</td>
<td>1</td>
<td>125</td>
<td>0.0033*</td>
</tr>
<tr>
<td>Bio-Rad HIV Ag-Ab Combo</td>
<td>90</td>
<td>8</td>
<td>1</td>
<td>130</td>
<td>0.0455*</td>
</tr>
<tr>
<td>Architect HIV Ag-Ab Combo</td>
<td>88</td>
<td>5</td>
<td>3</td>
<td>133</td>
<td>0.7237</td>
</tr>
</tbody>
</table>

* Significant difference; NR: non-reactive; R: reactive
### Ag/Ab Combo assays and second negative window

- BioPlex-C showed a second negative phase during seroconversion.

<table>
<thead>
<tr>
<th>Vendor ID</th>
<th>collection date</th>
<th>Roche V2.0 Viral load</th>
<th>BioPlex-C</th>
<th>ARCH</th>
<th>Combo</th>
<th>CHIV</th>
<th>DC</th>
</tr>
</thead>
<tbody>
<tr>
<td>9012-01</td>
<td>11/12/1997</td>
<td>1.75 x 10^5</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>NR</td>
</tr>
<tr>
<td>9012-02</td>
<td>11/14/1997</td>
<td>TND</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>9012-03</td>
<td>11/19/1997</td>
<td>&lt; 2 x 10^1 (BRD)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>9012-04</td>
<td>11/21/1997</td>
<td>1.02 x 10^2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>n/a</td>
</tr>
<tr>
<td>9012-05</td>
<td>11/26/1997</td>
<td>3.61 x 10^4</td>
<td>R</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>n/a</td>
</tr>
<tr>
<td>9012-06</td>
<td>11/28/1997</td>
<td>8.99 x 10^4</td>
<td>R</td>
<td>NR</td>
<td>R</td>
<td>R</td>
<td>n/a</td>
</tr>
<tr>
<td>9014-01</td>
<td>11/13/1997</td>
<td>2.90 x 10^4</td>
<td>R</td>
<td>NR</td>
<td>R</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>9014-02</td>
<td>11/15/1997</td>
<td>7.13 x 10^3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>9014-03</td>
<td>11/23/1997</td>
<td>2.20 x 10^2</td>
<td>NR</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>NR</td>
</tr>
<tr>
<td>9032-07</td>
<td>7/28/1998</td>
<td>4.49 x 10^4</td>
<td>R</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>9032-08</td>
<td>7/30/1998</td>
<td>2.76 x 10^4</td>
<td>R</td>
<td>NR</td>
<td>R</td>
<td>NR</td>
<td>R</td>
</tr>
<tr>
<td>9032-09</td>
<td>8/4/1998</td>
<td>2.81 x 10^4</td>
<td>NR</td>
<td>NR</td>
<td>R</td>
<td>NR</td>
<td>R</td>
</tr>
<tr>
<td>9032-10</td>
<td>8/11/1998</td>
<td>3.72 x 10^3</td>
<td>NR</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>NR</td>
</tr>
</tbody>
</table>
Antigen reactivity with BioPlex-C

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

<table>
<thead>
<tr>
<th>BioPlex-C</th>
<th>viral load copies/ml</th>
<th>n</th>
<th>mean</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>neg neg</td>
<td></td>
<td>32</td>
<td>7.3 x10^3</td>
<td>TND- 1.39 x10^5</td>
</tr>
<tr>
<td>pos neg</td>
<td></td>
<td>42</td>
<td>1.07 x10^6</td>
<td>85.8- &gt;10^7</td>
</tr>
<tr>
<td>pos pos</td>
<td></td>
<td>41</td>
<td>1.53 x10^6</td>
<td>TND- &gt;10^7</td>
</tr>
<tr>
<td>neg pos</td>
<td></td>
<td>56</td>
<td>1.26 x10^5</td>
<td>TND- 3.54 x10^6</td>
</tr>
</tbody>
</table>

pos = positive, neg = negative

Ag Ab n mean range
neg neg 32 7.3 x10^3 TND- 1.39 x10^5
pos neg 42 1.07 x10^6 85.8- >10^7
pos pos 41 1.53 x10^6 TND- >10^7
neg pos 56 1.26 x10^5 TND- 3.54 x10^6
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

HIV Diagnostics and Incidence Team

- Wei Luo
- Krystin A. Price
- William Fowler
- Vickie Sullivan
- Sarah Adams
- Michele Owen