2012
HIV Diagnostics Conference
Research Findings Relevant for the New HIV Testing Algorithm

The findings and conclusions in this presentations are those of the author and do not necessarily represent those of the Centers for Disease Control and Prevention. Or of the moderators.
### March 2011 to November 15, 2012

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL SAMPLES RECEIVED</td>
<td>14,559</td>
</tr>
<tr>
<td>UNSATISFACTORY SPECIMENS NOT TESTED</td>
<td>42</td>
</tr>
<tr>
<td>HIV COMBO 4(^{th}) GEN TESTED</td>
<td>14,517</td>
</tr>
<tr>
<td>HIV COMBO 4(^{th}) GEN NON-REACTIVE</td>
<td>14,238</td>
</tr>
<tr>
<td>HIV COMBO 4(^{th}) GEN REPEAT REACTIVE (RR)</td>
<td>279</td>
</tr>
<tr>
<td>HIV COMBO 4(^{th}) GEN REPEAT REACTIVE &amp; IFA POSITIVE</td>
<td>240</td>
</tr>
<tr>
<td>HIV COMBO 4(^{th}) GEN REPEAT REACTIVE &amp; IFA NEGATIVE</td>
<td>39 (30 sent for HIV-1 RNA test; 35 HIV-2)</td>
</tr>
<tr>
<td>HIV COMBO 4(^{th}) GEN REPEAT REACTIVE &amp; RNA POSITIVE</td>
<td>17</td>
</tr>
<tr>
<td>HIV COMBO 4(^{th}) GEN REPEAT REACTIVE &amp; RNA NEGATIVE</td>
<td>13</td>
</tr>
<tr>
<td>HIV COMBO 4(^{th}) GEN RR &amp; STATE LAB HIV-2 ANTIBODY NOT DETECTED</td>
<td>35</td>
</tr>
</tbody>
</table>
HIV IFA VS HIV MULTISпот
March 2011 to November 15, 2012

<table>
<thead>
<tr>
<th>Total Samples Tested</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFA Positive &amp; Multisпот Positive</td>
<td>25</td>
</tr>
<tr>
<td>IFA Negative and Multisпот Positive</td>
<td>1</td>
</tr>
<tr>
<td>IFA Inconclusive &amp; Multisпот Positive</td>
<td>4</td>
</tr>
<tr>
<td>IFA Negative &amp; Multisпот Negative</td>
<td>6</td>
</tr>
</tbody>
</table>
### Sensitivity Results in Seroconversion Samples

<table>
<thead>
<tr>
<th>PANEL ID</th>
<th>Members Tested</th>
<th>HIV-1 RNA Positive Samples</th>
<th>Bio-Rad GS HIV Combo Ag/Ab EIA</th>
<th>Abbott Architect HIV Ag/Ab Combo</th>
<th>Siemens HIV 1/O/2 Enhanced EIA</th>
<th>Ortho Anti-HIV 1+2 EIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRB951</td>
<td>6</td>
<td>4 (67%)</td>
<td>4 (67%)</td>
<td>4 (67%)</td>
<td>1 (17%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>HIV9077</td>
<td>24</td>
<td>17 (71%)</td>
<td>16 (67%)</td>
<td>16 (67%)</td>
<td>14 (58%)</td>
<td>14 (58%)</td>
</tr>
<tr>
<td>HIV9079</td>
<td>25</td>
<td>18 (72%)</td>
<td>17 (68%)</td>
<td>17 (68%)</td>
<td>15 (60%)</td>
<td>15 (60%)</td>
</tr>
<tr>
<td>Number</td>
<td>55</td>
<td>39</td>
<td>37/39</td>
<td>37/39</td>
<td>30/39</td>
<td>30/39</td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
<td></td>
<td>94.9 %</td>
<td>94.9 %</td>
<td>76.9 %</td>
<td>76.9 %</td>
</tr>
</tbody>
</table>
A Multicenter Performance Evaluation of the ADVIA Centaur HIV Ag/Ab Combo (CHIV) Assay on the ADVIA Centaur Immunoassay System

Saxton E¹, Baker L¹, Apple F², Murakami M², Schiff E³, de Medina M³, Turczyn J⁴, Chen J⁴, Dillon P¹, Levine R¹, Neaman I¹

¹ Siemens Healthcare Diagnostics Inc., Tarrytown, NY, U.S.
² Hennepin County Medical Center, Minneapolis, MN, U.S.
³ University of Miami Center for Liver Diseases, Miami, FL, U.S.
⁴ Siemens Clinical Laboratory, Berkeley, CA, U.S.
Performance of the VITROS Immunodiagnostic Products HIV Combo Assay*

Charles A. Noeson
Assay Research and Development

Ortho Clinical Diagnostics
a Johnson & Johnson company
*In Development
Sensitivity of assay reactivity during early HIV-1 infections relative to number of days before first positive WB

- Days before positive Western blot
  - 4th gen IA
  - 3rd gen IA
  - Rapid tests
  - 2nd gen IA
  - NAT

- Assays:
  - Determine Combo Ag+Ab (15.5)
  - BioRad Combo (18)
  - Architect Combo (20)
  - Vitros 3rd (14)
  - Insti (8)
  - Multisport (7)
  - AvioQ (6)
  - Unigold (5)
  - Oraquick (0)

- Sensitivity of assay reactivity during early HIV-1 infections relative to number of days before first positive WB.

- Days before positive Western blot:
  - 0
  - 5
  - 10
  - 15
  - 20
  - 25
Performance of the 4\textsuperscript{th} generation HIV testing algorithm for Multispot confirmation only

<table>
<thead>
<tr>
<th>MS Confirmation Scenario(^\dagger) (N=394)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WB, IB, NAAT</td>
<td>97.1</td>
<td>91.5</td>
<td>98.8</td>
<td>81.1</td>
</tr>
<tr>
<td>WB or IB only</td>
<td>96.8</td>
<td>86.0</td>
<td>97.9</td>
<td>79.6</td>
</tr>
<tr>
<td>NAAT for MS-negative only; WB, IB, NAAT for MS-dual HIV-1/2 only</td>
<td>97.1</td>
<td>91.5</td>
<td>98.8</td>
<td>81.1</td>
</tr>
</tbody>
</table>

\(^\dagger\) MS, Multispot; WB, Western blot (HIV-1); IB, Immunoblot (HIV-2); NAAT, Nucleic acid amplification test for HIV-1 or HIV-2
Correlation between HIV-1 RNA $\log_{10}$ copies/mL versus $\log_{10}$ S/CO for 12 acute infections + dilutions (*)

[Graph showing the correlation between HIV-1 RNA log10 copies/mL and Architect S/CO log10 values for 12 acute infections and dilutions. The graph includes a red circle highlighting a particular data point marked with an asterisk (*).]
PATIENTS WITHOUT HIV

100% negative predictive value

100% positive predictive value

PATIENTS WITH Acute HIV

100% sensitivity

100% specificity

Test Results

Frequency

Positive or negative?
Alaska is HUGE!!!
RESULTS (Sensitivity)

• Between 4/16/12 – 9/16/12 a total of **51,953** Abbott HIV-1/2 Combo CMIA were performed.

• 992 specimens were CMIA repeatedly reactive of which
  - 920 (1.8%) were Multispot HIV-1 reactive
  - 2 were Multispot HIV-1/2 nonreactive, HIV-1 NAAT reactive *(algorithm-defined acute cases)*
  - Sensitivity = 100% (922/922)

• 50,961 were CMIA nonreactive.
  • Abbott Specificity = 99.86% (50961/51031)
  • Algorithm Specificity = 99.99% (51030/51031)
  • PPV = 99.9% (922/923)
Turn Around Time in Days to Report HIV-1 Positive Results, Jan. – July 2012

Jan – March only 22% were reported in < 2 days compared to May – July 96%.

Number of Positive Results Reported

Laboratory Reporting TAT
## Clinical HIV Testing

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Interval</th>
<th>Number Tested</th>
<th>Reactives</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic Systems HIV-1/HIV-2 Plus O EIA (3rd Gen)*</td>
<td>Aug 2008 - Apr 2011</td>
<td>30,885</td>
<td>599</td>
<td>(1.94%)</td>
</tr>
<tr>
<td>Architect HIV Ag/Ab Combo (4th Gen)**</td>
<td>May 2011 - Jul 2012</td>
<td>15,076</td>
<td>394</td>
<td>(2.61%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46,061</td>
<td>993</td>
<td>(2.42%)</td>
</tr>
</tbody>
</table>

* Bio-Rad  
** Abbott
Multispot Results for EIA (3rd Gen) and CMIA (4th Gen) Reactive Samples

<table>
<thead>
<tr>
<th>MS Result</th>
<th>Number of Samples</th>
<th>Confirmatory Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non Reactive</td>
<td>50 (3rd Gen)</td>
<td>HIV-1 Viral Load</td>
</tr>
<tr>
<td></td>
<td>53 (4th Gen)</td>
<td></td>
</tr>
<tr>
<td>Reactive, HIV-1</td>
<td>882</td>
<td>WB* Pos 871</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WB* Ind 11</td>
</tr>
<tr>
<td>Reactive, HIV-2</td>
<td>3</td>
<td>IB** Pos 3</td>
</tr>
<tr>
<td>Reactive, HIV-1&amp;2 (Post-dilution)</td>
<td>5</td>
<td>IB** Pos 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IB** Neg 4</td>
</tr>
</tbody>
</table>

* WB: Bio-Rad Genetic Systems HIV-1 Western Blot (WB)
** IB: Focus Diagnostic HIV-2 Immunoblot (IB)
Conclusions

- The MS performed well as the confirmatory test for screening algorithms that used either 3\textsuperscript{rd} or 4\textsuperscript{th} generation HIV-1/2 assays.

- Weakly reactive HIV-2 MS, in the presence of HIV-1 MS, likely reflect cross reactivity with HIV-1 antibody.
Results (1)

- 570 analyzable specimens:
  - 220 WB-indeterminate
  - 350 WB-negative

- Specimens were reclassified as follows:
  - 512 (90%) as HIV-negative
  - 46 (8%) as HIV-1 positive (including 19 [3%] as acute HIV-1)
  - 2 (0.4%) as HIV-2 positive
  - 1 (0.2%) as HIV-positive, type undifferentiated

- 9 (1.6%) WB-indeterminate specimens were positive for HIV-1 by Multispot but APTIMA-negative.
  - These would have been considered positive under the new algorithm (APTIMA would not have been done)
Summary (1)

- 9% (49/570) of the EIA-reactive specimens were HIV positive applying the new HIV diagnostic algorithm:
  - 18% (39/220) of WB-indeterminate
  - 3% (10/350) of WB-negative

- 85% (485/570) negative by both Multispot and APTIMA
  - 69% (152/220) of WB-indeterminate
  - 92% (324/350) of WB-negative
Summary (2)

- 6% (36/570) Multispot HIV-1 reactive, APTIMA–negative
  - 9 (1.6%) WB-indeterminate with 2 reactive HIV-1 spots
  - 11 (1.9%) WB-indeterminate with 1 reactive HIV-1 spot
  - 16 (2.8%) WB-negative with 1 reactive HIV-1 spot
Multispot HIV-1 Reactive Results

Architect Reactive tested with Multispot
N=654

**HIV-1 Reactive**
- n=545 (83.3%)

**HIV Reactive but Undifferentiated**
- n=19 (1.7%)

**HIV-2 Reactive**
- n=0 (0%)

**Non-Reactive**
- n=90 (13.8%)

**Both HIV-1 Spots**
- n=536 (98.3%)

**Recombinant HIV-1 Spot only**
- n=6 (1.1%)

**HIV-1 Peptide Spot only**
- n=3 (0.6%)

**Western blot (n=388)**
- positive 384 (99.0%)
- indeterminate 3* (0.8%)
- negative 1* (0.2%)
  * NAAT reactive

**IFA (n=148)**
- positive 142 (95.9%)
- indeterminate 5* (3.4%)
- negative 1* (0.7%)
  * NAAT reactive
Multispot Non-Reactive

Architect Reactive tested with Multispot
N=654

- HIV-1 Reactive
  n=545 (83.3%)
- HIV Reactive but Undifferentiated
  n=19 (1.7%)
- HIV-2 Reactive
  n=0 (0%)
- Non-Reactive
  n=90 (13.8%)

NAAT reactive
n = 47 (52.2%)

NAAT negative
n = 43 (47.8%)
Multispot HIV-1 Reactive Tested with NAAT
New York City specimens only, September 2011 – 2012

Architect Reactive tested with Multispot
N=346

- HIV-1 Reactive
  - n=301 (87.0%)
  - NAAT reactive
    - n = 296 (98.3%)

- HIV Reactive but Undifferentiated
  - n=14 (4.0%)

- HIV-2 Reactive
  - n=0 (0%)

- Non-Reactive
  - n=31 (9.0%)

NAAT negative
n = 5 (1.7%)
## NAAT False Negative: Case Details

<table>
<thead>
<tr>
<th></th>
<th>Architect</th>
<th>Multispot</th>
<th>Rapid – Oraquick</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Reactive</td>
<td>HIV-1 Reactive</td>
<td>Reactive</td>
<td>New diagnosis, partner of one year known HIV positive, history of drug use, not asked about ART use, did not link to care</td>
</tr>
<tr>
<td>2</td>
<td>Reactive</td>
<td>HIV-1 Reactive</td>
<td>Reactive</td>
<td>New diagnosis, visiting from Caribbean, documented negative test in 2010</td>
</tr>
<tr>
<td>3</td>
<td>Reactive</td>
<td>HIV-1 Reactive</td>
<td>Reactive</td>
<td>Previous positive, diagnosed in 1999, re-establishing care, unclear if on ART, viral load 9 days after HIV testing undetectable</td>
</tr>
<tr>
<td>4</td>
<td>Reactive</td>
<td>HIV-1 Reactive</td>
<td>Reactive</td>
<td>Previous positive, diagnosed in 2008, refused interview, unknown if on ART, linked to care</td>
</tr>
<tr>
<td>5</td>
<td>Reactive</td>
<td>HIV-1 Reactive</td>
<td>Reactive</td>
<td>Previous positive, diagnosed in 2009, refused interview, unknown if on ART</td>
</tr>
</tbody>
</table>
## Results: Median Reagent Costs per Specimen
### Adjusted for Controls and Run Size

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Medium Volume</th>
<th>High Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reagent $/test</td>
<td>Adjusted† Reagent $/test (range)</td>
</tr>
<tr>
<td><strong>3G Advia, Bio-Rad, Vitros</strong></td>
<td>3.17</td>
<td>3.80 (1.76-10.29)</td>
</tr>
<tr>
<td><strong>4G Architect, Bio-Rad</strong></td>
<td>5.34</td>
<td>8.28 (4.39-13.37)</td>
</tr>
<tr>
<td><strong>Western blot Bio-Rad</strong></td>
<td>40.00</td>
<td>134.75 (32.31-167.10)</td>
</tr>
<tr>
<td><strong>Multispot‡</strong></td>
<td>17.32</td>
<td>18.04 (12.27-19.06)</td>
</tr>
<tr>
<td><strong>APTIMA‡</strong></td>
<td>40.00</td>
<td><strong>120.00</strong> (n/a)</td>
</tr>
</tbody>
</table>

†Adjusted for controls and run size
‡ Data from too few labs to calculate Multispot and APTMIA costs by specimen volume
# Results: Cost-effectiveness for a Cohort of 30,000 Specimens with 1% HIV Prevalence, 0.1% Incidence

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Testing Costs ($)</th>
<th>Incr Cost ($)</th>
<th>Infections Detected</th>
<th>Incr Effects</th>
<th>$ per Infection Detected</th>
<th>ICER($)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medium Volume Laboratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current 3G</td>
<td>273,000</td>
<td>-----</td>
<td>299.4</td>
<td>-----</td>
<td>912</td>
<td>Dominated**</td>
</tr>
<tr>
<td>New 3G</td>
<td>232,200</td>
<td>(40,800)</td>
<td>314.4</td>
<td>15 more</td>
<td>739</td>
<td>----</td>
</tr>
<tr>
<td>New 4G</td>
<td>326,100</td>
<td>$93,900</td>
<td>324.3</td>
<td>10 = 25</td>
<td>1,006</td>
<td>9,390</td>
</tr>
<tr>
<td><strong>High Volume Laboratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current 3G</td>
<td>165,570</td>
<td>-----</td>
<td>299.4</td>
<td>-----</td>
<td>553</td>
<td>Dominated**</td>
</tr>
<tr>
<td>New 3G</td>
<td>167,130</td>
<td>$1,560</td>
<td>314.4</td>
<td>15 more</td>
<td>532</td>
<td>Dominated**</td>
</tr>
<tr>
<td>New 4G</td>
<td>163,530</td>
<td>($3,600)</td>
<td>324.3</td>
<td>10 = 25</td>
<td>502</td>
<td>----</td>
</tr>
</tbody>
</table>

*ICER: Incremental Cost-Effectiveness Ratio represents cost per additional HIV infection identified

**Dominated – more costly, less effective than an alternative strategy
Limitations

- Convenience sample: costs might not be representative.
- Test costs vary and change frequently, particularly with the introduction of new tests and platforms.
- All models are wrong.
- How wrong do they have to be to not be useful?
Neither MS spot alone separates HIV positive and negative specimens
Quality Assurance is expensive.

1. The majority of specimens run for a second rapid in an RTA are run to comply with QA requirements
   - Quality Control
   - Proficiency Testing
   - Competency Assessment

2. Operators who use specimen types infrequently can be easily confused - particularly when they are under stress

3. CONCLUSION: It doesn’t make sense to make every site an RTA site
SOLUTION: Rapid-2-Rapid

- Solve the linkage problem - by connecting the second step in screening (verification) with the first step in connecting the HIV+ client into care!
Generations
"I can’t forgive you until you have apologised in front of the media."