Update on HIV Testing

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The views expressed in this presentation are those of the author and do not necessarily represent those of the Centers for Disease Control and Prevention
Outline

- Changes in HIV testing technology
- Detecting Acute HIV Infection
- HIV-2
- New HIV diagnostic testing algorithm: emphasis on sensitivity
- Follow-up testing
Evolution of HIV Tests

- **1\textsuperscript{st} generation**: whole viral lysate, detects IgG antibody
- **2\textsuperscript{nd} generation**: synthetic peptides, detects IgG antibody
- **3\textsuperscript{rd} generation**: detect IgM and IgG antibody
- **4\textsuperscript{th} generation**: detects IgM, IgG antibodies, p24 antigen

- “Combi” tests: detect both HIV-1 and HIV-2 antibodies
- Nucleic acid tests: detect HIV RNA
HIV Infection and Laboratory Markers

HIV RNA (plasma)

HIV p24 Ag

Infection

4th gen 3rd gen 2nd gen 1st gen

IgM

IgG

HIV Antibody

CLIA-Waived Point-of-Care Rapid HIV Tests

- OraQuick Advance
- Uni-Gold Recombigen
- INSTI
- Clearview Complete
- Clearview Stat Pak
New Rapid Tests
DPP HIV-1/2 Assay

- CLIA moderate complexity for serum, plasma, oral fluid
- “SampleTainer” = residual specimen after testing
- FDA-approved Dec 21, 2012
Dual Path Platform

Conjugate

Specimen
Determine Combo Rapid HIV 1/2 Ag/Ab Test

- CLIA moderate complexity
- Distinguishes Ag from Ab
- Whole blood, serum plasma
- FDA-approved August 2013
Rapid HIV Test Results without Rapid Test Kits
On-board Refrigeration of Multiple Different Assays

Random Access Multiplatform analyzers for HIV testing
Random Access Multiplatform analyzers for HIV testing

STAT sample requests without pausing
Results in <60 minutes
ADVIA® Centaur™ HIV 1/O/2 Enhanced (EHIV)

- Chemiluminescent immunoassay

- 3rd generation format
  - HIV-1: gp41, p24
  - HIV-2: gp36
  - group O

- Time to result <1 hour

- FDA-approved July 2006
Ortho VITROS ECi/ECiQ

- Chemiluminescent immunoassay
- 3rd generation format
  - HIV-1: gp41, gp120, p24
  - HIV-2: gp36
  - group O
- Time to result <1 hour
- Repeat only borderline results
- FDA-approved March 2008
Abbott Architect 4th Generation Ag/Ab Combo Assay

- Chemiluminescent immunoassay
- Detects p24 antigen and HIV antibody
- Time to result: 29 minutes
- FDA-approved June 22, 2010
Bio-Rad GS HIV Combo Ag/Ab EIA

- Microwell plate EIA

- 4th generation:
  - HIV-1: gp160
  - HIV-2: gp36
  - Group O

- p24 antigen

- FDA-approved July 25, 2011
- 26 seroconverters were analyzed with 14 tests
- 17 seroconverters with WB positive used for cumulative frequency analysis
Sequence of Test Positivity Relative to WB (plasma)

166 specimens, 17 Seroconverters - 50% Positive Cumulative Frequency


Luo et al, J Clin Virol 2013
HIV Infection and Laboratory Markers

- HIV RNA (plasma)
- HIV p24 Ag
- HIV Antibody

Days

0 10 20 30 40 50 60 70 80 90 100

Infection

4th gen
3rd gen
2nd gen
1st gen

Acute HIV Infection

Why Does It Matter?

- Sensitivity among frequently-tested MSM in Seattle

- 192 infected with HIV
  - 23 (12%) detected only by RNA
    - (15/16 tested detected by Ag/Ab immunoassay)
  - 169 (88%) detected by serum Ab immunoassay
  - 153 (80%) detected by oral fluid rapid test

- Stekler et al, Clin Inf Dis 2009
Performance of 4 antibody tests – Clinical Testing, San Francisco

<table>
<thead>
<tr>
<th>Test</th>
<th>Acute HIV</th>
<th>Established HIV</th>
<th>All HIV</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oraquick Oral</td>
<td>0/11</td>
<td>110/116 (94.8%)</td>
<td>110/127</td>
<td>86.6%</td>
</tr>
<tr>
<td>OraQuick fingerstick</td>
<td>0/18</td>
<td>226/228 (99.1%)</td>
<td>226/246</td>
<td>91.9%</td>
</tr>
<tr>
<td>Vironostika EIA</td>
<td>0/22</td>
<td>262/262 (100%)</td>
<td>262/284</td>
<td>92.3%</td>
</tr>
<tr>
<td>GS EIA</td>
<td>3/7 (27.3)</td>
<td>97/97 (100%)</td>
<td>100/104</td>
<td>96.2%</td>
</tr>
</tbody>
</table>

*Pilcher et al, PLoS One 2013*
Houston, Texas Hospitals, 2011-2013

3rd generation laboratory testing, 2 hospitals

- 238 repeatedly reactive EIA, Western blot negative or indeterminate
- Sent for NAT testing

- 26 (10.9%) positive = acute HIV infection
Policy Implications

Texas Department of State Health Services

- HIV testing must use blood-based specimens (finger stick or venipuncture).
- Confirmatory testing must be collected by venipuncture on-site immediately after a point-of-care (e.g., rapid) preliminary positive test result.
- After a reactive immunoassay, all indeterminate and non-reactive confirmatory tests must be automatically referred for a NAAT to determine if a client has an acute HIV Infection.

- Effective June 1, 2014
4th Generation Ag/Ab Assay vs. RNA

RNA+/ 3rd gen-negative specimens detected by 4th generation EIA:

- 38 of 46 (83%) – Australia*
- 10 of 14 (71%) – CDC AHI study**
- 51 of 61 (84%) – CDC panel***

- 4 days after RNA – 9 seroconversion panels***

* Cunningham P, HIV Diagnostics Conf 2007
** Patel P, CROI 2009
*** Owen M, CROI 2009
Phoenix ED Screening July 2011 through February 2013

- 4<sup>th</sup> gen screening of patients who had blood drawn
  - 15% of patients declined testing
  - 13,014 patients tested
  - 37 (0.3%) new HIV infections
    - 12 (32.4%) had Acute HIV Infection (antibody negative)

- Median viral load:
  - Acute infection: 3.6 million copies/ml
  - Established infection: 27,125 copies/ml
Limitations of Antibody Testing

- Antibody tests do not detect infection in \( \sim 10\% \) of infected persons at highest risk of transmission.

- Western blot confirmation is less sensitive during early infection than many widely used screening tests.

- Antigen/antibody combo tests now FDA-approved that can detect most antibody-negative persons during highly infections acute infection stage.
HIV-2 Infection

- **Remains uncommon in U.S., but**
  - Does not respond to NNRTIs, some PIs (first line therapy)
  - Undetectable by HIV-1 viral load tests

- **Misclassification by HIV-1 Western blot:**
  - 54/58 (93%) HIV-2 patients tested had positive HIV-1 WB (NYC)*
  - 97/163 (60%) HIV-2 cases reported had positive HIV-1 WB (CDC)**

- **HIV-2 often diagnosed after immunologic deterioration in patient with negative viral load**

*Torian et al, Clinical Infectious Disease 2010
**MMWR July 2011
CDC/APHL Proposed New HIV Testing Algorithm
4th generation HIV-1/2 immunoassay

(-)

HIV-1/2 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

NAT (+) NAT (-)

Acute HIV-1 infection Negative for HIV-1

NAT: nucleic acid test (e.g., RNA)
FDA-approved HIV-1/HIV-2 Antibody Differentiation Assay

Reactive Control  Recombinant HIV-1

Peptide HIV-2  Peptide HIV-1
Nucleic Acid Test (NAT) for Diagnosis

- APTIMA HIV-1 qualitative RNA assay is only NAT FDA-approved for diagnosis

- Clinicians can order HIV-1 viral load tests, but labs cannot use them as a reflex part of the algorithm

- APHL and CDC contracted 2 referral laboratories (NY State and FL) as reference laboratories for APTIMA from other public health labs
Implementation: Massachusetts
First 12 months

- 7,984 specimens tested
  - 258 (3.2%) positive for HIV-1
  - 1 (0.01%) positive for HIV-2
  - 8 (0.10%) acute HIV infections
    - 6 = EIA negative, WB negative
    - 2 = EIA reactive, WB indeterminate
Suggested Reporting Language for the HIV Laboratory Diagnostic Testing Algorithm

November 2013


(Search: APHL HIV Reporting Language)
Using Rapid HIV Testing Algorithms to Improve the Accuracy of HIV Testing, Receipt of Test Results, and Linkage to Care

- Delaney et al, CROI 2011
Intervention

- **Rapid test algorithm**
  - Clients with a preliminary-positive test have blood drawn for standard (offsite) confirmatory testing
  - Up to 2 additional rapid blood tests
  - 2 positive rapid tests = same day referral for HIV care

- Los Angeles: 4 sites   San Francisco: 5 sites
Comparison

- Rapid test with laboratory confirmation
  - Clients with a preliminary-positive test had blood drawn for standard offsite confirmatory testing
  - Appointment scheduled (usually for 7 days later) to receive confirmatory test results
  - Referral if confirmatory test positive

- Los Angeles: 12 sites    San Francisco: 11 sites
## Results

<table>
<thead>
<tr>
<th></th>
<th>Intervention Sites</th>
<th>Comparison Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>False-positive rapid test</td>
<td>N: 37</td>
<td>N: 124</td>
</tr>
<tr>
<td></td>
<td>%: 14.8%</td>
<td>%: 13.6%</td>
</tr>
<tr>
<td>Confirmed positive</td>
<td>N: 213</td>
<td>N: 791</td>
</tr>
<tr>
<td></td>
<td>%: 85.2%</td>
<td>%: 86.4%</td>
</tr>
<tr>
<td>Positive on multiple rapid tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N: 213*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%: 100.0%</td>
<td></td>
</tr>
<tr>
<td>Received results</td>
<td>N: 250</td>
<td>N: 430</td>
</tr>
<tr>
<td></td>
<td>%: 100.0%</td>
<td>%: 47.0%</td>
</tr>
</tbody>
</table>

*Includes one client who tested (false) negative on the 2\textsuperscript{nd} test before testing positive on a third rapid test
In Care (CD4/VL) within 3 Months

1004 HIV-infected persons eligible for linkage

181 Tested anonymously

48 Reside out of surveillance jurisdiction

775 HIV-infected individuals for engagement in care analysis

Only 179 from intervention sites
Estimates of Time from Diagnosis to First Reported CD4 or Viral Load

Proportion with evidence of care engagement

Comparison, received referral

Comparison, no referral

Intervention

Logrank p < .0001
Conclusions

- **PPV: rapid test algorithm 100%; single rapid test 85%**

- **Engaged in care <90 days:**
  - 67% of clients who received referral
  - 50% of clients who did not return for confirmatory results or receive referral

- **Referral to care after reactive rapid test is essential**
Dear Colleague,

The purpose of this letter is to clarify questions and concerns raised by grantees and sub-grantees of the Health Resources and Services Administration (HRSA) Ryan White HIV/AIDS Program (RWHAP) and Centers for Disease Control and Prevention (CDC) about HIV testing and linkage to care. Pursuant to the legislative intent of the RWHAP and the Administration’s National HIV/AIDS Strategy (NHAS), it is imperative that individuals who are potentially eligible for RWHAP-funded services receive an accurate HIV diagnosis and are quickly linked to RWHAP-funded medical care.
- There is no legislative requirement for a “confirmed” HIV diagnosis prior to linkage to RWHAP-funded medical care, nor is there any specific statutory or program requirement related to the use of Western blot.

- Having positive results from only one HIV antibody test should not be a barrier to linkage to care to a RWHAP-funded clinic or other HIV care providers.
Three Options for Referral

- Refer only after positive supplemental test
  - Some patients will seek care without 2nd test result

- Refer to care after 2 reactive rapid tests
  - Positive/negative rapid test results still require follow-up testing because small percentage are HIV-positive

- Refer to care after one reactive rapid test
  - Small percentage patients will be HIV-negative
  - Arrange specific intake for additional testing
Additional Information

- **2011 Journal of Clinical Virology Supplement**
  - *Open access:*
  - [www.journalofclinicalvirology.com](http://www.journalofclinicalvirology.com)

- **2013 Journal of Clinical Virology Supplement**
  - *Open access:*
  - [www.journalofclinicalvirology.com](http://www.journalofclinicalvirology.com)