Overview of HIV Testing Practices and Technology

2019 HIV Diagnostics Conference
March 25th, 2019

Michele Owen, Ph.D
National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention
Centers for Disease Control and Prevention

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Tradenames are used for informational purposes and does not constitute an endorsement by CDC.
### HIV TRANSMISSIONS IN 2016

<table>
<thead>
<tr>
<th>% OF PEOPLE WITH HIV</th>
<th>STATUS OF CARE</th>
<th>ACCOUNTED FOR X% OF NEW TRANSMISSIONS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>15%</td>
<td>didn’t know they had HIV</td>
<td>38%</td>
</tr>
<tr>
<td>23%</td>
<td>knew they had HIV but weren’t in care</td>
<td>43%</td>
</tr>
<tr>
<td>11%</td>
<td>in care but not virally suppressed</td>
<td>20%</td>
</tr>
<tr>
<td>51%</td>
<td>taking HIV medicine and virally suppressed</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Values do not equal 100% because of rounding

SOURCE: Vital Signs, 2019  
https://www.cdc.gov/vitalsigns/end-hiv/images/vs-infographic-end-hiv1.jpg
Testing Technology
1985
• Viral Lysate IgG HIV-1 EIA

1987
• Western Blot approved as supplemental test

1989
• p24 Antigen EIA
• CDC MMWR 1st HIV diagnostic algorithm

1990
• HIV-2 EIA
• EIA approved for DBS

1991
• Recombinant/Peptide HIV-1/HIV-2 EIA

1992
• HIV-1 IFA approved as supplemental test
• HIV-1 Rapid Test (not CLIA waived)
• IgG/IgM HIV-1/HIV-2 EIA

1994
• HIV-1 Oral fluid collection device and oral fluid EIA
1996
• Oral fluid Western blot
• Urine HIV-1 EIA
• HIV-1 Home specimen collection diagnostic system
• Quantitative viral load test

2002
• Rapid IA CLIA waived for whole blood and plasma

2003
• EIAs Include Group O antigen
• CLIA waived rapid for whole blood

2004
• CLIA waived rapid IA for oral fluid
• Rapid EIA to differentiate between HIV-1 and HIV-2

2006
• Random access microparticle HIV1/2/0 chemiluminescence test
• HIV-1 nucleic acid test approved for diagnostic applications
• Revised recommendations for HIV testing in clinical settings

2008
• CLIA waiver requirements revised

2010
• HIV1/2 antigen/antibody combo test approved
2012
- CLIA waived rapid IA that gives almost immediate results
- Over the counter rapid IA for use with oral fluid

2013
- Rapid antigen/antibody IA

2014
- CLIA waived rapid antigen/antibody IA
- Dual Path supplemental assay to distinguish HIV-1 from HIV-2
- Updated guidelines for laboratory testing for HIV
- Pre-exposure prophylaxis (PrEP) guidelines issued

2015
- Multiplex flow immunoassay for detection and differentiation of HIV p24 antigen and antibodies to HIV-1 (group M and group O) and/or HIV-2

2017
- Minor modification to guidelines for laboratory testing for HIV to include rapid Ag/Ab assay with plasma

2018
- PrEP guidelines updated
- FDA advisory committee meeting on HIV test down-classification
## CDC Preferred Nomenclature for Initial Tests

<table>
<thead>
<tr>
<th>Test Category</th>
<th>Analyte targets</th>
<th>Previous Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag/Ab combo laboratory-based</td>
<td>HIV-1 p24 Ag, IgM/IgG Ab to HIV-1/HIV-2</td>
<td>4&lt;sup&gt;th&lt;/sup&gt; generation</td>
</tr>
<tr>
<td>Ag/Ab combo rapid test (POC)</td>
<td>HIV-1 p24 Ag, IgM/IgG Ab to HIV-1/HIV-2</td>
<td>4&lt;sup&gt;th&lt;/sup&gt; generation</td>
</tr>
<tr>
<td>IgM/IgG-sensitive laboratory-based</td>
<td>IgM/IgG Ab to HIV-1/HIV-2</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; generation</td>
</tr>
<tr>
<td>IgM/IgG-sensitive rapid test (POC)</td>
<td>IgM/IgG Ab to HIV-1/HIV-2</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; generation</td>
</tr>
<tr>
<td>IgG-sensitive tests (lab-based or POC)</td>
<td>IgG Ab to HIV-1 or HIV-1/HIV-2</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;/2&lt;sup&gt;nd&lt;/sup&gt; generation</td>
</tr>
</tbody>
</table>
Time to Test Reactivity

- Seroconversion panel data used to compare tests in context of time since RNA reactivity
  - Inter-test reactivity interval (ITRI)
- Eclipse period simulated from published data and combined with ITRI data
- Why?
  - Valuable to testing providers for interpreting negative HIV test results
  - Counseling individuals on when to retest after an exposure
<table>
<thead>
<tr>
<th>Days Since Infection</th>
<th>Analyzer</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.3</td>
<td>RNA</td>
</tr>
<tr>
<td>11.5</td>
<td>RNA</td>
</tr>
<tr>
<td>29.1</td>
<td>RNA</td>
</tr>
<tr>
<td>33.0</td>
<td>RNA</td>
</tr>
<tr>
<td>44.3</td>
<td>Ag/Ab</td>
</tr>
<tr>
<td>13.0</td>
<td>Ag/Ab</td>
</tr>
<tr>
<td>17.8</td>
<td>Ag/Ab</td>
</tr>
<tr>
<td>23.6</td>
<td>Ag/Ab</td>
</tr>
<tr>
<td>18.4</td>
<td>IgM/IgG</td>
</tr>
<tr>
<td>23.1</td>
<td>IgM/IgG</td>
</tr>
<tr>
<td>28.8</td>
<td>IgM/IgG</td>
</tr>
<tr>
<td>49.5</td>
<td>IgM/IgG</td>
</tr>
<tr>
<td>28.5</td>
<td>IgG*</td>
</tr>
<tr>
<td>33.4</td>
<td>IgG*</td>
</tr>
<tr>
<td>39.2</td>
<td>IgG*</td>
</tr>
<tr>
<td>58.2</td>
<td>IgG*</td>
</tr>
</tbody>
</table>

**Key**

- Median
- 25th
- 75th
- 99th
- 75th
- 99th
- Median
- 25th
- 75th

**Eclipse**

- Oral Fluid EIA
- HIV RNA (plasma)
- HIV p24 Ag
- HIV Antibody
- IgM
- IgG

**Analyte**

- HIV Antibody
- HIV p24 Ag
- IgM
- IgG

**Delaney et al CID, 2016**

**Luo et al J Clin Virol, 2013**
Resources

HIV/AIDS

Laboratory Tests

This section focuses on FDA-approved diagnostic HIV tests for use in moderate and high complexity laboratories.

Laboratory Testing Guidance

- New Item January 2018 2018 Quick Reference Guide: Recommended laboratory HIV testing algorithm for serum or plasma specimens
- Updated January 2019 APHL Suggested Reporting Language for the HIV Laboratory Diagnostic Testing Algorithm
- Full Version of the Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations
- Technical Update on HIV-1/2 Differentiation Assays, August 2016
- Technical Update: Use of the Determine HIV 1/2 Ag/Ab Combo Test with Serum or Plasma in the Laboratory Algorithm for HIV Diagnosis

FDA Approved HIV Tests

- Updated June 2018 Advantages and Disadvantages of Different Types of HIV tests
- Updated March 2018 Laboratory Screening Tests
- Laboratory Screening Tests
- Updated February 2019 Supplemental Tests for Laboratory Settings
- Moderate Complexity Rapid HIV Tests for Clinical Settings
- Updated June 2018 CLIA waived rapid HIV tests

https://www.cdc.gov/hiv/testing/laboratorytests.html
Laboratory Algorithm
Objectives of 2014 Laboratory Algorithm

- Improve diagnosis of acute HIV infection
- Accurate diagnosis of HIV-2
- Decrease turn-around time for results
- No substantial change in cost for testing

https://stacks.cdc.gov/view/cdc/23447
Determine HIV 1/2 Ag/Ab Combo Test in the Laboratory Algorithm for HIV Diagnosis

- CDC and APHL continue to recommend an instrumented, laboratory based antigen/antibody (Ag/Ab) HIV immunoassay as the first step in the laboratory algorithm.
- Determine can detect infection earlier than IgM/IgG sensitive (antibody-only) immunoassays when used with plasma\textsuperscript{1,2}
- Laboratories in which instrumented Ag/Ab testing is not feasible, Determine can be used with serum/plasma as the first step in the laboratory algorithm.
- Laboratories using Determine are advised to acknowledge the limitations of the testing procedure when reporting results.
- Ag only reactivity can be followed with parallel testing of Ab (differentiation assay) and NAT
  - Data needed for a definitive recommendation and potential algorithm updates.
- \texttt{https://stacks.cdc.gov/view/cdc/48472}

\textsuperscript{1}Delaney et al, \textit{Clinical Infectious Diseases}, 2016, \textsuperscript{2}Masciotra et al. \textit{Journal Clinical Virology}, 2013 and 2017
Figure 2: HIV Laboratory Testing Algorithm in Serum/Plasma (modified from 2014 algorithm figure and CDC Quick Reference Guide)

HIV-1/2 antigen/antibody immunoassay^1

Nonreactive

Reactive

HIV-1/HIV-2 antibody differentiation immunoassay

HIV-1 Positive
HIV-1 (+) HIV-2 (-)

HIV-2 Positive^2
HIV-1 (-) HIV-2 (+)

HIV Positive Untypable
HIV-1 (+) HIV-2 (+)

HIV Negative
HIV-1 (-) HIV-2 (-)

HIV Indeterminate
HIV-1 (Ind) HIV-2 (Ind)

HIV-1 Indeterminate
HIV-1 (Ind) HIV-2 (-)

HIV-2 Indeterminate^3
HIV-1 (-) HIV-2 (Ind)

HIV-1 NAT

Detected

Undetected

HIV-1 antigen and HIV-1/HIV-2 antibodies were not detected^4

Positive for HIV-1 Antibodies^5

Positive for HIV-2 Antibodies^6

Positive for HIV-1 and HIV-2 Antibodies^7

Positive for acute HIV-1 infection^8

Negative for HIV-1^9

---

a. The FDA-approved single-use rapid HIV-1/HIV-2 antigen/antibody immunoassay can be used as the initial assay in the laboratory HIV testing algorithm for serum or plasma. If any instrumented antigen/antibody test is available, it is preferred due to its superior sensitivity for detecting HIV during acute infection. b. This includes specimens reported as HIV-2 positive with HIV-1 cross-reactivity. c. Per the Genium Package Insert, specimens with this final assay interpretation should be retested with a new cartridge. If the final assay interpretation is again HIV-2 indeterminate, it should be reported as such and followed with an HIV-1 NAT. d. If recent HIV exposure is suspected or reported, conduct HIV-1 NAT or request a new specimen and repeat the algorithm according to CDC Guidance. e. Link patient to HIV medical care and provide appropriate prevention counseling. f. Link patient to HIV medical care and provide appropriate prevention counseling immediately to expedite prevention practices. g. If a negative HIV-1 NAT result and repeatedly HIV-2 indeterminate or HIV indeterminate antibody differentiation immunoassay result should be referred for testing with a different validated supplemental HIV-2 test (antibody test or NAT) if available. Alternatively, redraw and repeat algorithm in 2-4 weeks to assess HIV-2 infection.
Point of Care and Self Testing
Considerations for POC Testing

- Viable option for locations/populations where lab testing is not feasible
- Successfully used to improve linkage
- Assay characteristics
  - High sensitivity and specificity in established infections and no ART
  - Whole blood assays detect infections later than laboratory assays
  - Oral fluid assays will likely miss acute infections and some early infections
- Guidance available
  https://www.cdc.gov/hiv/testing/nonclinical/index.html
Self-testing

- Recent systematic review by Stevens et al\(^1\) indicates the following:
  - Generally high sensitivity and specificity of assays but with wide ranges in some studies
  - Acceptability generally high
  - Most individuals were capable of performing self-testing
    - Education level and language were linked to lower performance
    - To date little evidence of harm related to self-testing
- WHO recommended self-testing in 2016\(^2\)
- One FDA approved assay in the U.S. \(^3\)
  - FDA analysis predicted public health benefit
- RCT in U.S. indicate feasibility and potential for public health benefit \(^4\)
- Barriers in U.S. \(^1,4\)
  - Cost
  - Assay choice

\(^1\)Stevens et al AIDS Behav 2018  \(^2\)https://www.who.int/hiv/pub/vct/hiv-self-testing-guidelines/en/
\(^3\)http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm091994.htm
\(^4\) MacGowan et al. AIDS and Behav 2018
Testing in the Context of PrEP

- Evidence that testing in the context of PrEP can result in ambiguous results
  - False negative – altered window periods for test reactivity
  - False positive- technical issues, repeated testing
- Resistance can develop if PrEP is initiated or continued in infected individuals
- Resolution of ambiguous results important to prevent harm
  - Proper Counseling
  - Additional testing
- PrEPline 855-448-7737 (11 am-6pm EST)
  - Report ambiguous results
  - Advice on patient management related to ambiguous results
Rapid/POC/TNT/Dual Claim NATs

• Available outside the U.S., but none are FDA approved
  • AlereQ HIV-1/2 Detect
  • Xpert HIV-1 Qual
  • SAMBA II Qual
  • COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Qualitative Test v2.0 (CE)
  • Aptima HIV-1 Quant Dx Assay (CE-IVD)

• Potential for earlier diagnosis and to conduct NAT in more locations
• Potential to impact current laboratory testing algorithm
• Potential to impact care
• Status for the U.S.?
Summary

• Diagnostic assays continue to evolve

• Current HIV Laboratory Testing Algorithm recommended June 2014 with minor updates in 2018

• New data on Inter-test reactivity interval (ITRI) should improve interpretation of negative test results and counseling for retesting

• Rapid and HST will likely play an important role in “Ending the HIV Epidemic”

• Testing in the context of PrEP introduces the potential for new opportunities and challenges

• NAT technology available outside the U.S. would likely improve HIV testing in the U.S.
Thanks!

Questions?
mowen@cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Tradenames are used for informational purposes and does not constitute an endorsement by CDC.