

The Role of 4th Generation HIV Combo Immunoassays in the New HIV Diagnostic Algorithm: Impact on Timely Diagnosis and Linkage to Care in Florida's Public Health Population



APHL Annual Meeting - Industry Workshop
Sponsored by Abbott Laboratories
Little Rock, AR
June 2, 2014

Berry Bennett, MPH
Retrovirology Section Chief
FL. Bureau of Public Health Laboratories,
FDOH
berry.bennett@FLHealth.gov

ADD-00003360



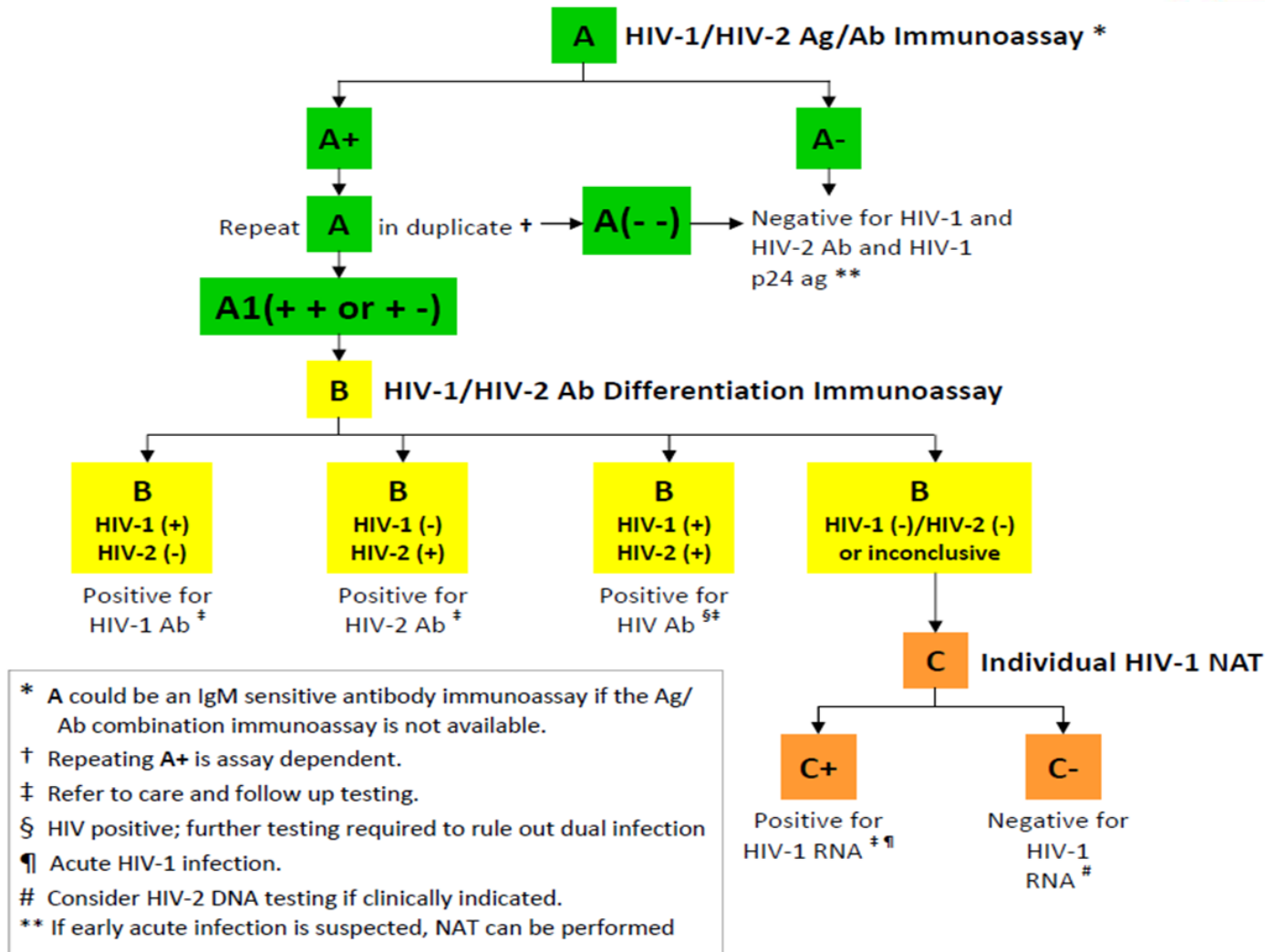
This presentation is sponsored by, and on behalf of, Abbott Diagnostics Division and content related to Abbott product is consistent with all applicable FDA requirements.

Characteristics of the Proposed HIV Diagnostic Algorithm



- Detects acute as well as established HIV infections
- Differentiates HIV-1 from HIV-2
- Allows for timely results to facilitate initiation of care – “more same day reporting”
- Eliminates most, but not all, indeterminate and inconclusive results.

APHL/CDC HIV-1/2 Diagnostic Algorithm Template



4th Generation Immunoassays



Options for Test A

- Simultaneous qualitative detection of HIV-1 p24 antigen and antibodies to HIV-1 (Groups M and O) and HIV-2 in human serum or plasma.

- Abbott Architect HIV Ag/Ab Combo chemiluminescent assay (CIA), June 2010.



Refer to next slide for intended use and important safety information

- BioRad HIV Combo Ag/Ab EIA, July 2011.





Intended Use and Important Safety Information:

The ARCHITECT HIV Ag/Ab Combo assay is a chemiluminescent microparticle immunoassay (CMIA) for the simultaneous qualitative detection of human immunodeficiency virus (HIV) p24 antigen and antibodies to HIV type 1 (HIV-1 group M and group O) and/or type 2 (HIV-2) in human serum and plasma (EDTA and heparin). The ARCHITECT HIV Ag/Ab Combo assay is intended to be used as an aid in the diagnosis of HIV-1/HIV-2 infection, including acute or primary HIV-1 infection. The assay may also be used as an aid in the diagnosis of HIV-1/HIV-2 infection in pediatric subjects (i.e., children as young as two years of age) and in pregnant women. An ARCHITECT HIV Ag/Ab Combo reactive result does not distinguish between the detection of HIV p24 antigen, HIV-1 antibody, or HIV-2 antibody.

The ARCHITECT HIV Ag/Ab Combo is not intended for use in screening blood or plasma donors.

The effectiveness of ARCHITECT HIV Ag/Ab Combo for use in screening blood or plasma donors has not been established. However, this assay can be used as a blood donor screening assay in urgent situations where traditional licensed blood donor screening tests are unavailable or their use is impractical.

This product requires the handling of human specimens. Human sourced materials should be considered potentially infectious and handled in accordance with the OSHA Standards. This product contains sodium azide: material and its container must be disposed of in a safe way. Assay results should be interpreted in conjunction with the patient's clinical presentation, history, and other laboratory results. If the results are inconsistent with clinical evidence, additional testing is suggested to confirm the result. The performance of this assay has not been established for individuals younger than two years of age.

4th Generation Rapid Test



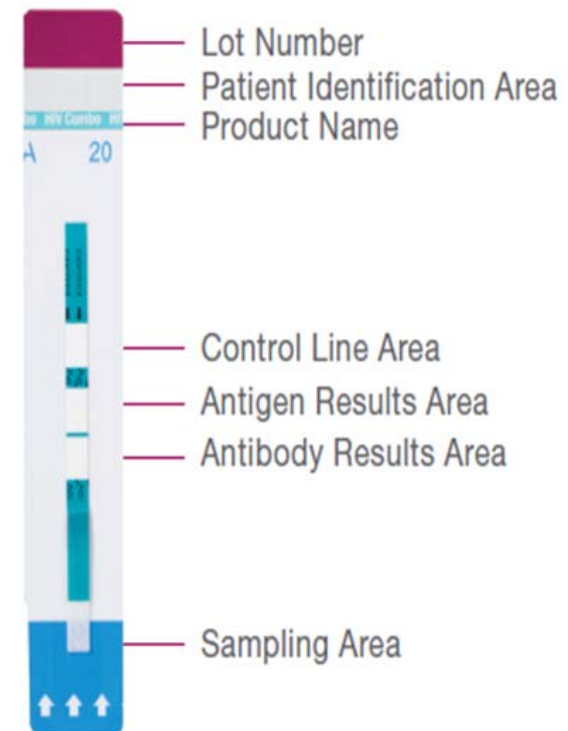
Data currently does NOT support this device for Test A

Alere Determine™ HIV-1/2 Ag/Ab Combo

- FDA approved 8/2013 (moderate complexity)
- Lateral flow methodology
- Time to results = 20 minutes
- Approved for fingerstick and venous whole blood, serum and plasma.
- PI Sensitivity 99.9%
- PI Specificity 99.6 – 99.8%

Reference

Masciotra S, et al. Performance of the Alere Determine™ HIV-1/2 Ag/Ab Combo Rapid Test with specimens from HIV-1 seroconverters from the US and HIV-2 infected individuals from Ivory Coast. J Clin Virol: August 1 2013.



ADD-00003360

Possible HIV-1/HIV-2 Differentiation Immunoassays



Options for Test B

Not currently available in the U.S.

FDA approved, March 2013

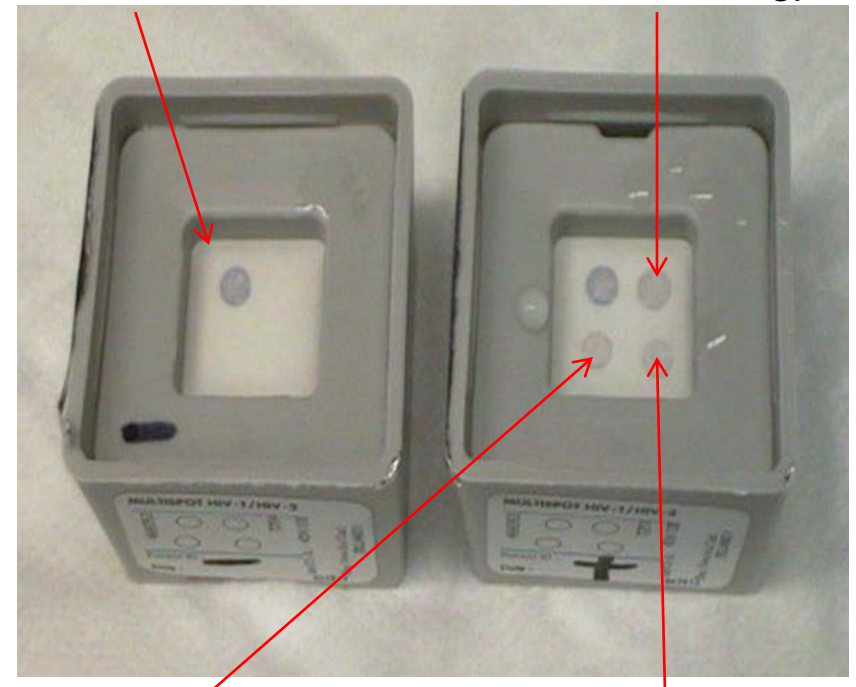


Non-FDA approved

- 1 gp36
- 2 gp160
- 3 gp120
- 4 gp41
- 5 gp24

Serum Control

Recombinant HIV-1 gp41



Peptide HIV-2 gp36

Peptide HIV-1 gp41

ADD-00003360



Multispot HIV-1/HIV-2 Rapid Test

Intended use change approved by FDA, March 2013

Complexity: Moderate

1. NAME AND INTENDED USE

The Multispot HIV-1/HIV-2 Rapid Test is a single use qualitative immunoassay to detect and differentiate circulating antibodies to Human Immunodeficiency Virus Types 1 and 2 (HIV-1, HIV-2) in fresh or frozen human serum and plasma. This rapid HIV-1/HIV-2 test kit is intended as an aid in the diagnosis of infection with HIV-1 and/or HIV-2 in fresh or frozen human serum or plasma. This test is suitable for use in multi-test algorithms designed for statistical validation of **an HIV screening test result or as part of an HIV-1/HIV-2 diagnostic algorithm that includes differentiation of HIV-1 and HIV-2 antibodies**

Interpretation for Diagnostic Testing Algorithm

Nonreactive



Label

Only the Procedural Control Spot shows purple color development. The 3 Test Spots show no color development. Test result is interpreted as negative for HIV-1 and HIV-2 antibodies. Additional, more specific supplemental testing is recommended, including HIV nucleic acid testing (NAT).

Reactive



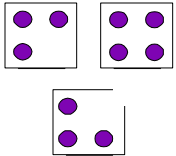
HIV-1 POSITIVE

The Procedural Control Spot shows purple color development and **both** the recombinant HIV-1 Spot and the HIV-1 Peptide Spot show purple color development. Test result is interpreted as Positive for HIV-1 antibodies



HIV-2 POSITIVE

The Procedural Control Spot shows purple color development. The HIV-2 Peptide Spot shows purple color development. Test result is interpreted as Positive for HIV-2 antibodies

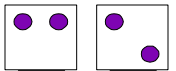


HIV Positive Undifferentiated

The Procedural Control Spot shows purple color development. The HIV-2 Peptide Spot shows purple color development as well as one or both HIV-1 Spots. In this case, the specimen may be tested by additional methods which allow for differentiation between HIV-1 and HIV-2. See diutional procedure which follows.



Indeterminate

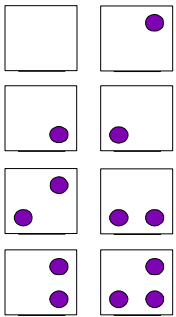


HIV-1 INDETERMINATE

The Procedural Control Spot shows purple color development and either the recombinant HIV-1 Spot or the HIV-1 Peptide Spot show purple color development, but not both HIV-1 Spots. Test result is interpreted as Indeterminate for HIV-1 antibodies and further testing is recommended.

Invalid

Do not report any results



If no color develops in the Procedural Control Spot, regardless of color development anywhere else on the membrane, the results are **INVALID**. (See examples.)

If the background on the membrane is dark and interferes with the interpretation of the spots, the results are invalid. In addition, if there are stray purple marks or discoloration that interfere with reading the spots, the assay should be repeated. Repeat the assay, and if results are still invalid collect a fresh sample or test by another method.



HIV-1 Nucleic Acid Amplification Tests (NAAT)



Options for Test C

- **Only one HIV-1 RNA test is FDA-approved for use as an aid in the diagnosis of HIV-1 infection**
 - APTIMA® HIV-1 RNA Qualitative Assay (Gen-Probe)
 - Approved for use with plasma and serum
 - Result is 'RNA Detected/Not detected'
- **HIV-1 RNA Viral Load assays are FDA approved for patient monitoring, i.e. assess prognosis, monitor effects of therapy**
 - Not intended as a diagnostic test to confirm the presence of HIV-1 infection
 - Approved for use with plasma only
 - Laboratories would need to validate viral load test for use as a diagnostic test and for use with serum

Process for Developing New HIV Testing Algorithms for the U.S.

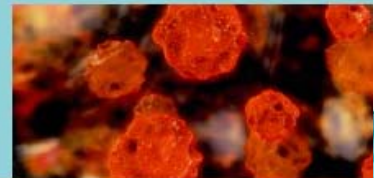
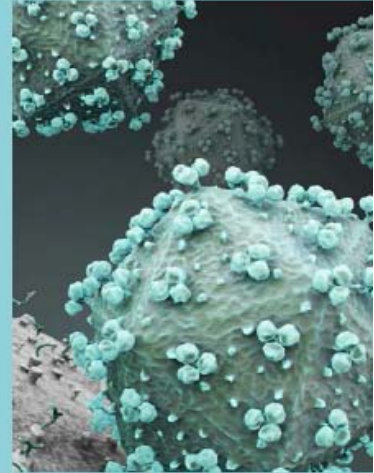
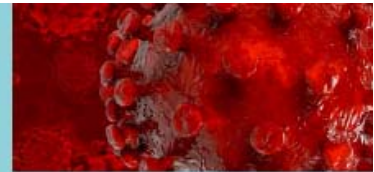


- ✓ APHL/CDC HIV Steering Committee (2006)
- ✓ Algorithm Workgroups [Point of contact (POC) and Laboratory]
Goal = Develop **multiple** acceptable HIV testing algorithms, i.e., a menu of options
- ✓ APHL & NASTAD Public Health Surveys
- ✓ 2007 HIV Diagnostics Conference (December 5-7, Atlanta)
- ✓ Preparation of the **Status Report**, released April 2009 at www.aphl.org/hiv/statusreport
- ✓ Status Report promotion at national conferences
- ✓ 2010 HIV Diagnostics Conference (March 24-26, Orlando)
- ✓ **Release of the CLSI Guidelines¹, July 2011**
- ✓ **CDC Dear Colleague letter to Surveillance Coordinators, Nov. 18, 2011**
- ❑ Each state must examine their case reporting and Ryan White eligibility criteria
- ❑ Ongoing data gathering: retrospective and prospective
- ✓ CDC Interim Guidance – MMWR June 21, 2013
- ✓ 2012 HIV Diagnostic Conference (Dec. 12-14, Atlanta)
- ❑ Final CDC Recommendations to follow mid 2014?

¹ Criteria for Laboratory Testing and Diagnosis of Human Immunodeficiency Virus Infection: Approved Guidelines. Clinical and Laboratory Standards Institute, M53-A.

www.aphl.org

Suggested Reporting Language for the HIV Laboratory Diagnostic Testing Algorithm

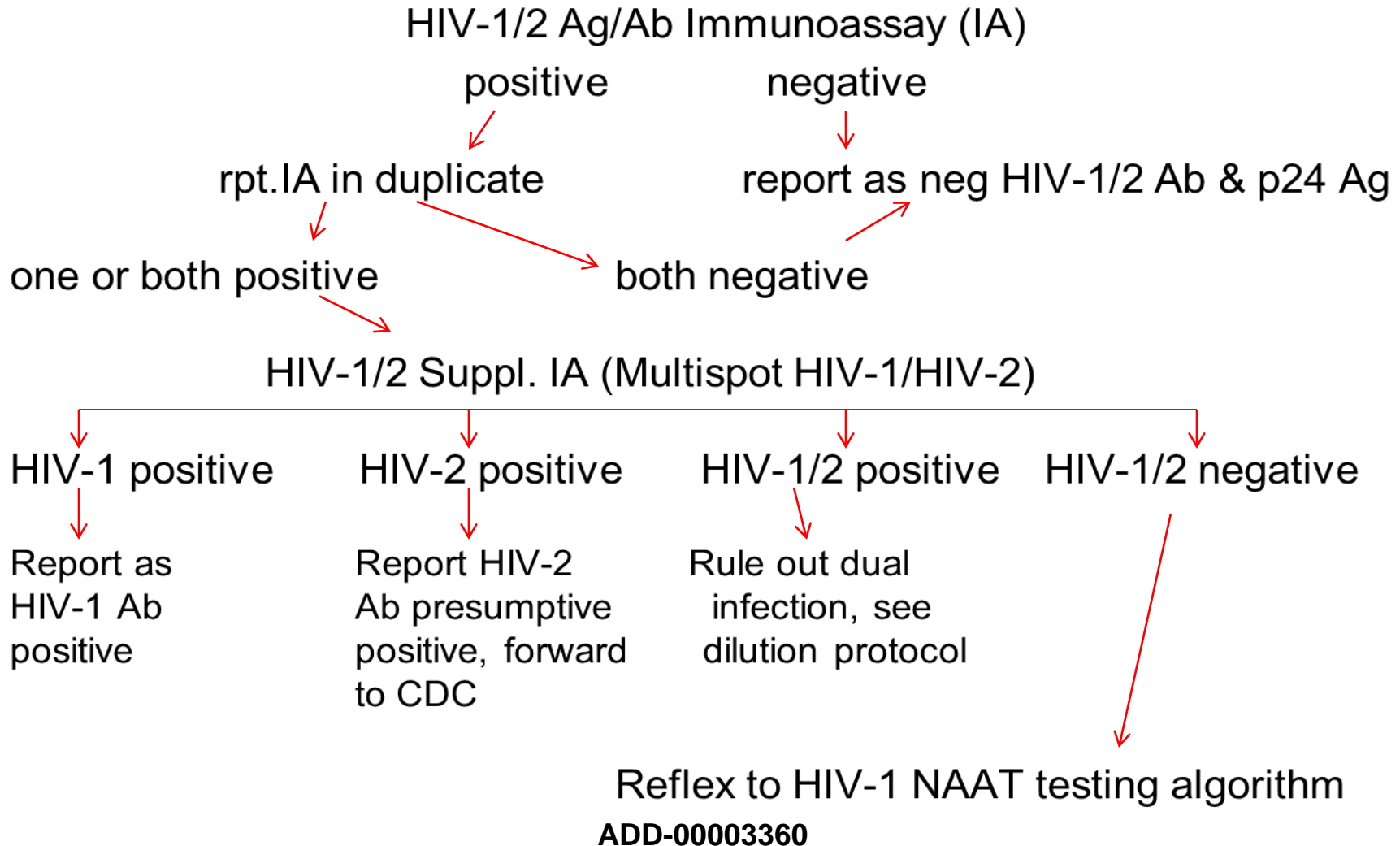


November 2013

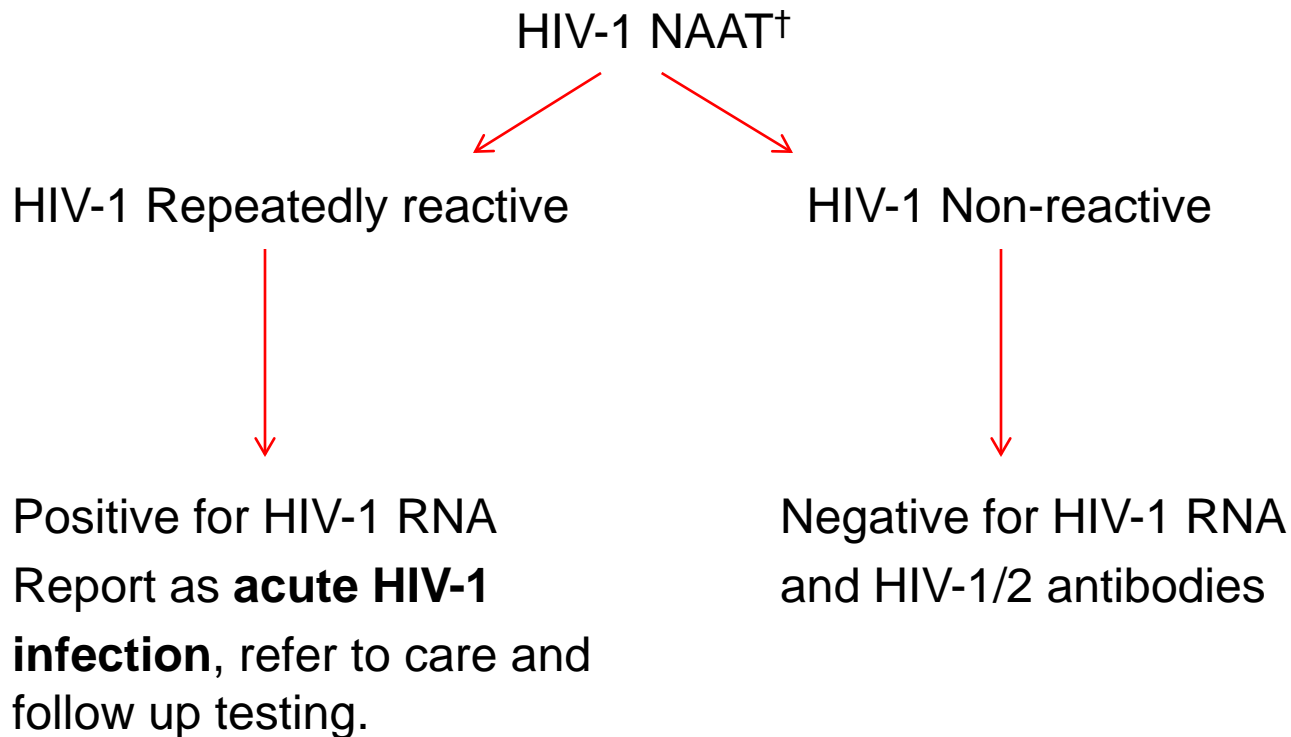


ADD-00003360

FBPHL Blood-based HIV-1/2 Testing Algorithm (April 16, 2012)



FBPHL Blood-based HIV-1/2 Testing Algorithm (cont.)



[†]FDA approved qualitative NAAT assay preferred.

FBPHL – 2013 Performance Jacksonville & Miami PHLs



- n = 120,465 **blood** specimens w/seropositivity = 1.8%
- 4th generation Abbott HIV-1/2 Ag/Ab Combo Performance;
sensitivity = 100% (2,194/2,194)
specificity = 99.9% (118,186/118,271) [PI claim 99.77% (99.62-99.88%)]
- New algorithm performance [MS nr (82) or IND (3) & NAAT nonreactive (85)];
specificity = 100% (118,268/118,268) assumes ARV naïve & no elite
controllers. 3 (MS IND, NAAT nr) previous positive on ART excluded.
- **14 Algorithm-defined HIV-1 acute infections detected**, 1 per 8,600 screens
and 0.6% (14/2,194) of our confirmed positive cases.
 - Combo **r/r**, MS **nonreactive**, qual RNA NAAT **reactive**
 - Only 3 were pre-screened by a rapid test, **all nonreactive**.
 - Detected in (12) counties; Dade, Broward, Palm Beach, Duval, Hillsborough,
Pinellas, Polk, Seminole, Escambia, Volusia, Nassau and Lake.
- No HIV-2 cases detected.

ADD-00003360

Resolve of Indeterminate Multispot HIV-1/HIV-2 Results?



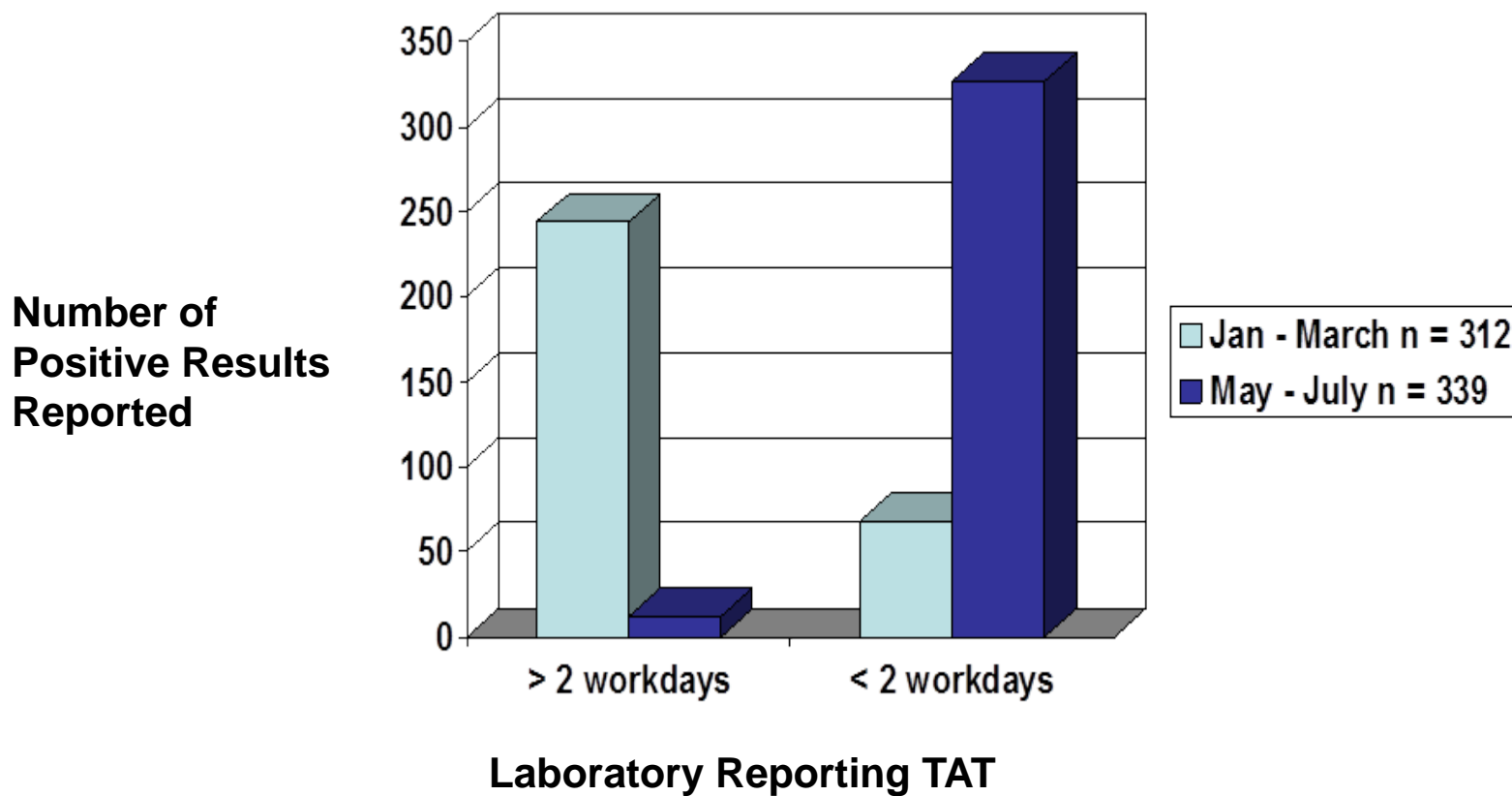
Specimen ID	Abbott Combo	Multispot HIV-1/2	APTIMA HIV-1	ART
J13084515	1.8, 2.0, 1.7	HIV-1 Recomb +	Reactive	unknown
J13063350	68.4, 67.6, 67.5	HIV-1 Recomb +	Reactive	Yes*
J13038296	12.6, 13.7, 14.1	HIV-1 Recomb +	Reactive	unknown
J13033939	1.2, 1.3, 1.1	HIV-1 Recomb +	QNS	unknown
M13016908	1.3, 1.3, 1.4	HIV-1 Recomb +	Reactive	Yes, PrEP
J13033679	14.6, 14.4, 14.0	HIV-1 Recomb +	Nonreactive	Yes*
M13001783	19.2, 17.8, 18.0	HIV-1 Recomb +	Nonreactive	Yes*
M13019333	9.1, 9.2, 9.4	HIV-1 Recomb +	Nonreactive	Yes*

* Previous positive HIV-1 Ab

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%.

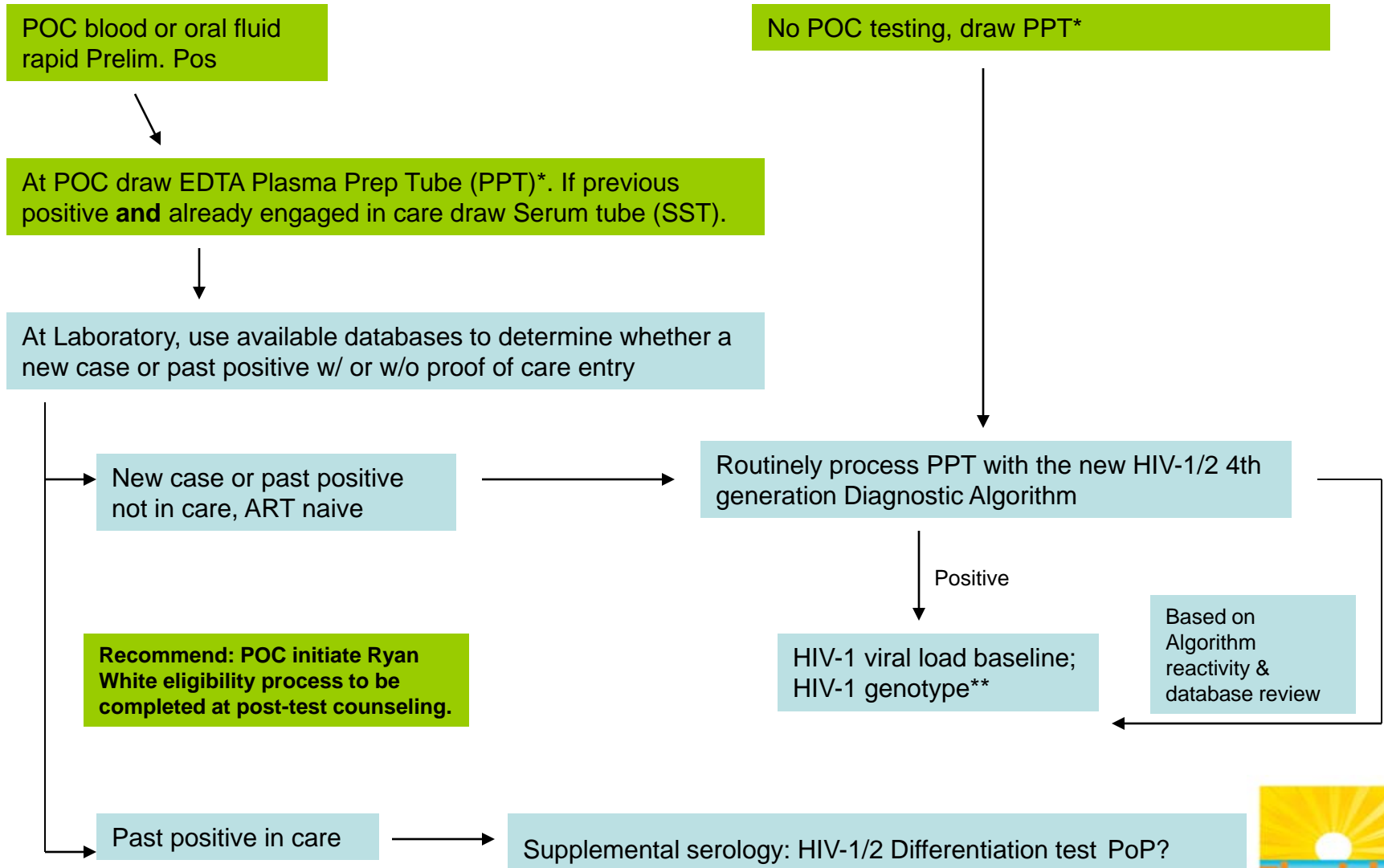


Alternative Algorithms?



- Individual or pooled NAAT on seronegative specimens (reflex testing). *Extends reporting TAT, may not be cost-effective.*
- Traditional algorithm with supplemental NAAT option instead of Western Blot. *Fewer AIs detected and may require reflex differentiation testing to rule out HIV-2 when HIV-1 NAAT is nonreactive.*
- Algorithms for oral fluid and dried fluid spot (DFS) specimens.
- “Bridge algorithms” (POC – laboratory – clinical management)

Single Staging for Acute and Early HIV Infections: Integration of Point-of-Contact (POC), Laboratory and Clinical Care Services



* Centrifuge PPT within 4-6 hours of collection, freeze & send frozen or on cold packs overnight priority

**HIV-1 “real-time” genotype or NGS preferred

ADD-00003360



Technology Vital to Bridging HIV-1 Diagnostics and Linkage to Care



- “Real Time” viral load testing:

- Flexible batch sizes
- High specimen throughput
- Same day reportable results



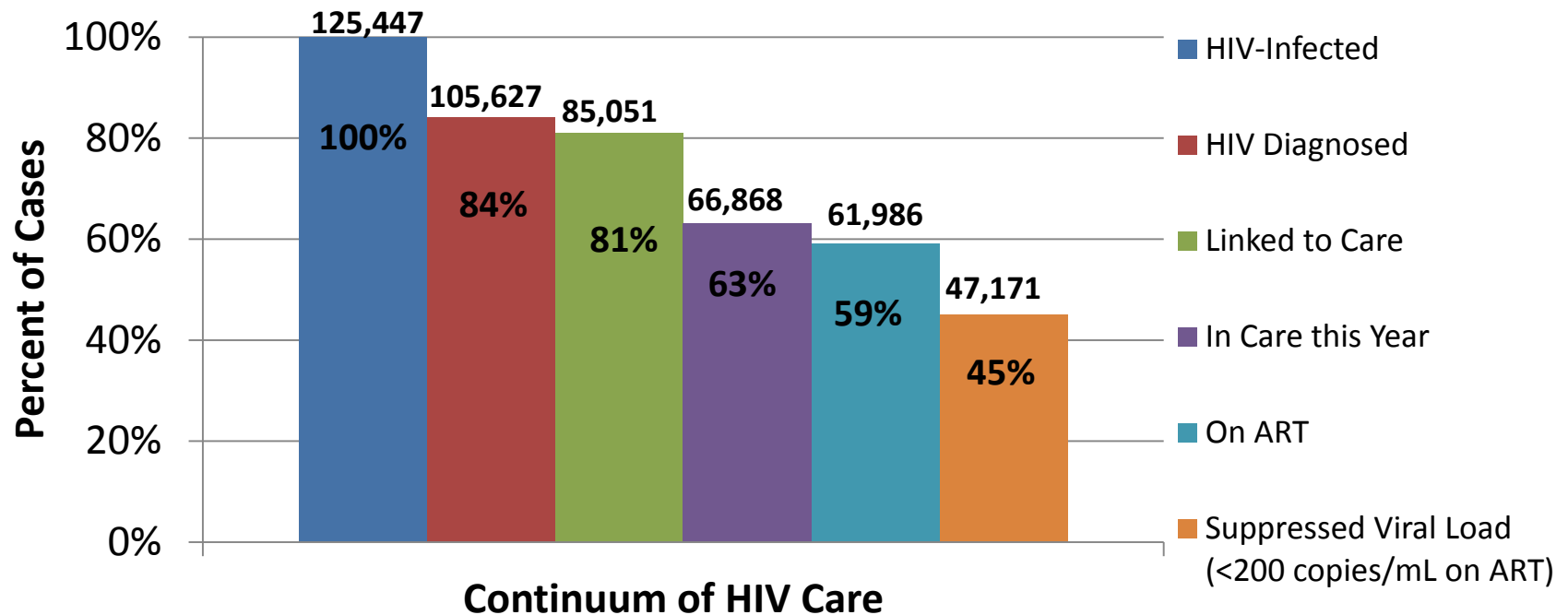
- Next Generation Sequencing (NGS) or Multiplex Sequencing ??

- cost-effective
- regular updates to gene library and prevailing ARV drugs/classes
- Same day reportable results



ADD-00003360

Number and Percentage of HIV-Infected Persons Engaged in Selected Stages of The Continuum of HIV Care — Florida, 2012



- HIV-infected=HIV diagnosed cases divided by 84.2% (to account for 15.8% national estimated unaware of their status in Florida).
- HIV Diagnosed=Number of cases known to be alive and living in Florida through 2012, regardless where diagnosed, as of 06/30/2013
- Linked to Care (**Ever in Care**) =Based on calculated data of persons living with HIV disease in Florida (regardless of where diagnosed) **who ever had a CD4 or Viral load test in the eHARS dataset** . (National estimates are 77%).
- In Care this Year=Based on Unmet need calculations as prescribed by HRSA, for persons living with HIV in Florida (regardless of where diagnosed) and having at least 1 HIV-related care service involving either a VL or CD4 test, or a refill of HIV-related RX. (National estimates for in care are 57%).
- On ART=Estimated 92.7% of In care this year in Florida per MMP (National estimates are 88%)
- Suppressed VL=Estimated 76.1% on ART are in care this year in Florida per MMP (National estimates are 77%)

ADD-00003360



HIV-1 Acute Infection Case Study



- 52 y/o male self-referred on 12/18/12 to a central Florida county health department with a high risk profile (MSM with unprotected multiple anonymous partners within the last 12 months). Blood collected 12/18/12.
- Laboratory findings;
 - Date received at FBPHL Jacksonville 12/20/12
 - Abbott HIV-1/2 Ag/Ab **repeatedly reactive** (S/CO = 585,576,585)
 - Multispot HIV-1/2 **nonreactive**
 - APTIMA HIV-1 RNA (NAAT) **reactive** (s/co = 27.0)Reported as an algorithm-defined HIV-1 acute infection on 12/21/12
- Subsequent blood (EDTA plasma) draw on 12/21/12.
 - 12/28/12 HIV-1 Viral load = 8,422,500 RNA copies/ml blood.
 - 12/28/12 HIV-1 genotype = wild type
- Diagnostic TAT = 3 days (patient unable to pinpoint risk to calculate Abbott detection window, but we estimate infection at 15-22 days prior to 12/18/12).
- *Clinical baseline TAT = 10 days* **ADD-00003360**

HIV Testing Algorithm Information



- HIV Testing Algorithms: A Status Report (5/2009)
<http://www.aphl.org/hiv/statusreport> (historical perspective)
- 2012 HIV Diagnostics Conference: <http://www.hivtestingconference.org>
- CLSI M53-A, Criteria for Laboratory Testing and Diagnosis of HIV-1 Infection, June 2011. (Includes algorithms utilizing assays available outside the US as well as those FDA approved)
- Original papers and review articles assembled in Special Supplement of *J Clin Virol*, December 2011 and December 2013



Commentary

Establishing the diagnosis of HIV infection: New tests and a new algorithm for the United States

Bernard M. Branson*, Jonathan Mermin

National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, 1600 Clifton Road, Mailstop D-21, Atlanta, GA 30333, USA

- CDC recommendations anticipated mid 2014.

ADD-00003360

Thank you & Questions??



ADD-00003360