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Nucleic Acid Testing by Public Health Referral Laboratories for Public Health Laboratories Using the U.S. HIV Diagnostic Testing Algorithm

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Abstract

Background—Many public health laboratories adopting the U.S. HIV laboratory testing algorithm do not have a nucleic acid test (NAT), which is needed when the third-or fourth-generation HIV screening immunoassay is reactive and the antibody-based supplemental test is non-reactive or indeterminate.

Objectives—Among public health laboratories utilizing public health referral laboratories for NAT conducted as part of the algorithm, we evaluated the percentage of screening immunoassays needing NAT, the number of specimens not meeting APTIMA (NAT) specifications, time to APTIMA result, the proportion of acute infections (i.e., reactive APTIMA) among total infections, and screening immunoassay specificity.

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Study Design—From August 2012 to April 2013, 22 laboratories enrolled to receive free APTIMA (NAT) at New York or Florida public health referral laboratories. Data were analyzed for testing conducted until June 2013.

Results: Submitting laboratories conducted a median of 4,778 screening immunoassays; 0 to 1.3% (median 0.2%) needed NAT. Of 140 specimens received, 9 (6.4%) did not meet NAT specifications. The median time from specimen collection to reporting the 11 reactive NAT results was ten days, including six days from receipt in the submitting laboratory to shipment to the referral laboratory. Acute infections ranged from 0 to 12.5% (median 0%) of total infections. Third- and fourth-generation immunoassays met package insert specificity values.

Conclusions—Public health referral laboratories provide a feasible option for conducting NAT. Reducing the time from specimen collection to submission of specimens for NAT is an important step toward maximizing the public health impact of identifying acute infections.

Keywords

HIV; algorithms; nucleic acid amplification test; diagnostic tests

Background

The HIV diagnostic testing algorithm recommended by the Centers for Disease Control and Prevention (CDC) and the Association of Public Health Laboratories (APHL) includes the use of a nucleic acid test (NAT) for specimens with a repeatedly reactive fourth-generation immunoassay and a non-reactive or indeterminate supplemental antibody test that differentiates HIV-1 from HIV-2. [1] If the NAT is negative, there is no evidence of HIV infection, and the result likely occurred due to a false-positive initial immunoassay. Fourth-generation immunoassays, such as the ARCHITECT HIV Ag/Ab Combo (Abbott Diagnostics, Chicago, Illinois) (ARCHITECT) and the GS HIV Combo Ag/Ab EIA (Bio-Rad Laboratories, Redmond, WA) (GS Combo), appear to perform with high specificity, [2–4] so false-positive results should be rare. If the NAT is reactive, there is evidence of acute infection. Identification of acute infections enables timely intervention to treat infected persons and curb onward transmission. [5, 6]

Only one NAT is Food and Drug Administration (FDA)-approved for diagnostic use, the APTIMA HIV-1 RNA Qualitative Assay (APTIMA, Hologic GEN-PROBE, San Diego, CA). Low testing volumes in many laboratories make it impractical to maintain the test due to cost and required technical expertise. [7] The CDC and APHL conducted a demonstration project in which two public health laboratories provided NAT referral services for public health laboratories using the recommended algorithm.

Objectives

We assessed whether submitting laboratories adhered to APTIMA specimen handling instructions, the time to provision of APTIMA results, the proportion of acute infections, and the specificity of the third- and fourth-generation screening immunoassays.

Study Design

New York State Department of Health's Wadsworth Center and the Florida Department of Health, Bureau of Public Health Laboratories were selected to serve as NAT referral laboratories because of their experience using APTIMA. APHL member laboratories using the laboratory algorithm with a repeatedly reactive third- or fourth-generation immunoassay and a non-reactive or indeterminate antibody supplemental test and without access to NAT were invited to participate at no cost. Although not preferred, third-generation immunoassays are listed as an alternative to fourth-generation immunoassays in the algorithm, [8] and Western blots and immunofluorescence assays are included as alternatives to supplemental antibody tests that differentiate HIV-1 from HIV-2. Between August 2012 and April 2013, 22 public health laboratories enrolled to send serum or plasma that required NAT to the referral laboratories. We examined data from enrollment until June 2013. During that period, 15 public health laboratories used fourth-generation immunoassays: seven used ARCHITECT and eight used GS Combo. Six laboratories used third-generation immunoassays: five used GS HIV-1/HIV-2 Plus O EIA (Bio-Rad Laboratories, Redmond, WA) (GS Plus O) and one used ADVIA Centaur HIV1/O/2 Enhanced (Ortho-Clinical Diagnostics, Tarrytown, NY) (ADVIA). One laboratory switched from a third-generation (GS HIV-1/HIV-2 Plus O EIA (Bio-Rad Laboratories, Redmond, WA)) to a fourth-generation immunoassay (ARCHITECT). For supplemental testing, eight laboratories used an HIV-1/HIV-2 differentiation test, ten used an HIV-1 Western blot, three used both, and one used an HIV-1 immunofluorescence assay and an HIV-2 Western blot.

The New York referral laboratory reported APTIMA results to the submitting laboratory by telephone or fax, and mailed a report. The Florida laboratory returned APTIMA results to the submitting laboratory by secure fax, and sent an email about the fax.

By submitting laboratory, we reported the number of specimens needing NAT. Nucleic acid tests, such as APTIMA, have more restrictive criteria for usage than serologic tests. We evaluated the proportion not meeting package insert requirements. We assessed the proportion of acute infections among total infections in each submitting laboratory. We conducted a sensitivity analysis for acute infections among total infections to assess the maximum proportion of acute infections. In this analysis, we considered specimens eligible for NAT testing that did not receive it, as well as submitted specimens with reactive NAT, to be acute infections. The occurrence of false-positive screening test results impacts how often NAT is needed. We calculated the specificity of each screening immunoassay by submitting laboratory. We conducted a sensitivity analysis that represented the worst case scenario for specificity, in which specimens with false-positive screening assay results based on NAT, and those eligible for NAT that did not receive it, were considered to have false-positive results. Finally, since timely provision of results among those with acute infection is paramount, we assessed the time from specimen collection to reporting of results, by APTIMA result.

Results

Specimens needing NAT

Submitting laboratories conducted between 486 and 39,257 third or fourth-generation immunoassay tests (median=4,778) (Table 1). From 0 % to 1.3% (median=0.2%) of specimens tested in each submitting laboratory needed NAT. Of those 290 specimens, 140 (48.3%) were submitted to the referral laboratories. The median specimen volume sent was 600μL.

Specimen adequacy for NAT

Of 140 specimens submitted, 9 (6.4%) were insufficient for testing because blood was stored for greater than 3 days before centrifugation (n=6), or because serum was held for more than 8 days at 4°C or above in the submitting laboratory (n=3).

Infections during the study period

Laboratories reported between 8 and 460 total HIV infections (Table 1). The proportion of acute infections among total infections ranged from 0 to 12.5% (median=0%). According to the sensitivity analysis, the maximum proportion of acute infections among total infections ranged from 0 to 36.4% (median=12.9%). The highest percentage was from the laboratory with eight total infections. There was no evidence of testing more than one specimen from persons identified with acute infection, based on the laboratory information systems in New York, and given that no two specimens tested in Florida came from the same laboratory.

Screening assay specificity

The median specificity for all assays was > 99.9% (Table 2). The specificity confidence interval for all screening immunoassays overlapped with or was higher than that listed in the package insert (not shown), except for one 'worst case' estimate for specificity for the GS HIV-1/HIV-2 Plus O EIA (98.7%).

Time to APTIMA results

The time from specimen collection to APTIMA result reporting was 11 days for those with non-reactive results and 10 days for those with reactive results (Table 3). The time from specimen receipt at the submitting laboratory to shipment to the referral laboratory was the biggest lag, and took six days. Referral laboratories tested specimens with APTIMA within two days.

Discussion

During the study, 22 laboratories using the recommended HIV diagnostic testing algorithm enrolled to receive NAT, which is indicative of the need for alternative NAT sources for public health laboratories. Approximately 0.2% of specimens tested needed NAT, and third- and fourth-generation immunoassays performed with high specificity. Thus, it may not be cost-effective for public health laboratories to implement NAT in-house. Most specimens submitted to public health referral laboratories were suitable for APTIMA testing. Eleven

acute infections were identified, some of which occurred in areas with low rates (i.e., <1%) of established infection.

The time from specimen collection to release of results from the referral laboratory was ten days for specimens from persons with acute infection, and there may have been subsequent delays in getting results to infected persons. Test results should be returned quickly to maximize the benefit of identifying persons with acute infection by linking them to care and treatment, counseling them to reduce risk behaviors that lead to transmission, and so that their partners can be offered testing. [9, 10] Although acute infections constituted less than 13% of infections for any laboratory, early infections are linked with a disproportionate number of transmissions relative to established infections, due to high viral loads during that period. [6, 11] The number of days the specimens remained in the submitting laboratory before shipment to the referral laboratory accounted for most of the delay. Some of this time reflected testing with the initial and supplemental IAs; whether specimens were held after testing until shipment to the referral laboratory is unknown. Time to shipment to the referral laboratory should decrease if laboratories using the Western blot adopt the HIV-1/HIV-2 rapid test. Specimens were swiftly processed and tested in the referral laboratories. However, in one case, staffing shortages, which were resolved, caused a 12-day processing time for a NAT non-reactive specimen.

Public health laboratories using the recommended algorithm may need sources of NAT other than public health referral laboratories. They may be able to partner with local laboratories implementing NAT, [12] which will require establishing methods for payment, and ensuring that partner laboratories maintain quality assurance, and return results rapidly. Commercial laboratories can provide a diagnostic NAT, but may be costly or have long turnaround times. If a quantitative HIV-1 NAT is FDA-approved for diagnostic use, laboratories will be able to run diagnostic testing as well as monitor disease progression and treatment, but this may not be cost-effective for laboratories that do not routinely perform tests to follow clinical status. Alternatively, persons with discordant results needing NAT could be referred to a clinical setting for resolution of infection status since a quantitative NAT can be ordered by a physician. Finally, HIV-1 nucleic acid tests are in development that may be conducted at the point of care, which would expedite the provision of results to persons with acute infection, and, likely reduce costs. [13–15]

Almost half of the specimens needing NAT were not submitted to a referral laboratory. Multiple specimens needing NAT may have come from the same individual, and so one NAT would sufficiently resolve infection status. Participating laboratories and testing programs should work together to identify the reasons for specimens not receiving NAT, as persons being tested may be acutely infected. The reasons specimens were not submitted for NAT were not recorded, but likely included specimen storage outside of test specifications, insufficient residual volumes, and persons not returning to submit an additional specimen. With the use of the recommended algorithm, increased serum or plasma is needed from all persons tested in case NAT is required, so that delays associated with subsequent specimen collections are avoided. Specimens must be held according to the specifications for all tests conducted in the algorithm. This may require modifying specimen collection protocols and apprising phlebotomy and laboratory staff of the changes. Plasma is needed if a doctor

orders a quantitative nucleic acid test, but APTIMA can be used with serum or plasma. The updated CDC/APHL guidance recommends that 2mL of serum or plasma be collected to conduct all assays in the algorithm. [1]

There were some limitations to our study. The conditions of the specimens at the collection site were unknown. In addition, this project did not capture whether the submitting laboratories that used only the HIV-1 Western blot for supplemental testing sent specimens with a reactive third-or fourth-generation assay and a negative or indeterminate HIV-1 Western blot and a negative HIV-1 NAT for further HIV-2 testing, as recommended in CDC/APHL guidance. [1]

Overall, most specimens received by the public health referral laboratories met APTIMA package insert requirements and turnaround time at the referral laboratories was rapid. However, overall time from specimen collection to reporting of test results for specimens from persons with acute infections was suboptimal to expedite care and services, and to prevent transmission. Laboratories using the recommended algorithm should work to complete all aspects of testing, referral and reporting of specimens in a timely manner to obtain the maximum public health benefit. Alternative NAT sources should also be examined so that the infection status of persons with discordant results can be resolved quickly.

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Table 1

HIV test results during the study period[a] for 22 public health laboratories using the recommended laboratory algorithm [1] and participating in the nucleic acid testing referral program

Public health Lab	Screening Immunoassay	Immuno-assays conducted	Percent established HIV infections[b]	Number, percent needing APTIMA	Total number of adequate specimens[c] submitted for APTIMA testing	Percent acute infections[d] of total HIV positive[e] (%)	Percent acute infections of total HIV positive--sensitivity analysis[f] (%)
1	ARCHITECT	7,973	1.0%	16 (0.2%)	1	0%	16.3%
2	ARCHITECT				3[g]		
3	GS Combo	1,467	0.5%	4 (0.3%)	1	12.5%	36.4%
4	GS Combo	486	19.3%	0	0	0%	0%
5	ARCHITECT	39,257	1.2%	76 (0.2%)	28	0.7%	10.0%
6	ARCHITECT	2,115	2.0%	5 (0.2%)	3	2.4%	6.8%
7	ARCHITECT	4,584	0.7%	9 (0.2%)	7	0%	5.7%
8	GS Plus O	11,557	0.1%	15 (0.1%)	3	0%	41.4%
9	GS Plus O	882	0.8%	11 (1.3%)	2	0%	56.3%
10	GS Plus O	3,025	0.3%	1 (0.03%)	1	0%	0%
11	GS Combo	7,032	0.6%	10 (0.1%)	4	0%	12.2%
12	GS Combo	2,590	5.8%	1 (0.04%)	0	0%	0.7%
13	GS Combo	5,845	0.4%	5 (0.09%)	2	0%	12.5%
14	GS Plus O until 1/2013, then ARCHITECT	30,952	0.8%	60 (0.2%)	24	0.8%	13.3%
15	ARCHITECT	4,342	0.7%	6 (0.1%)	2	0%	11.8%
16	GS Combo	7,299	0.1%	3 (0.04%)	1	0%	18.2%
17	GS Plus O	33,814	0.4%	26 (0.08%)	7	0.8%	13.7%
18	ADVIA[g]				8[h]		
19	GS Combo	4,971	0.3%	7 (0.1%)	5	0%	13.3%
20	GS Combo	4,485	2.7%	8 (0.2%)	8	0.8%	0.8%
21	GS Plus O	12,714	0.6%	19 (0.2%)	19	0%	0%
22	ARCHITECT	2,407	1.7%	8 (0.3%)	2	2.4%	14.9%

Public health Lab	Screening Immunoassay	Immuno-assays conducted	Percent established HIV infections[b]	Number, percent needing APTIMA	Total number of adequate specimens[c] submitted for APTIMA testing	Percent acute infections[d] of total HIV positive[e] (%)	Percent acute infections of total HIV positive--sensitivity analysis[f] (%)
Overall	N/A	Median 4,778	Median 0.7%	Total 290 (Median 0.2%)	131	Median 0%	Median 12.4%

[a] Study period: From enrollment (August 2012 to April 2013, depending on laboratory) until June 30, 2013

[b] Established HIV infections= reactive immunoassay and positive supplemental antibody test (e.g., HIV-1/HIV-2 differentiation immunoassay, Western blot, or IFA). % established infections= number of established infections of total immunoassays conducted.

[c] Adequate specimens are those that met package insert specifications.

[d] Acute infection=reactive third- or fourth-generation immunoassay, negative or indeterminate antibody supplemental test and reactive NAT.

[e] Total HIV positive= Number of established infections plus number of acute infections

[f] In the sensitivity analysis, in addition to NAT reactive specimens, specimens eligible for NAT testing that were not tested using NAT were considered to be acute infections.

[g] Laboratory did not send data to complete table elements. 1 of 3 specimens sent for NAT was acutely infected.

[h] Laboratory did not send data to complete table elements. 0 of 8 specimens sent for NAT were acutely infected

Table 2

Specificity of third- and fourth-generation immunoassays in 19 public health laboratories[a] participating in the nucleic acid testing referral program

Immunoassay (Laboratories)	Median Specificity[b] (Minimum, Maximum)	Median Specificity, Sensitivity Analysis[c] (Minimum, Maximum)
ARCHITECT HIV Ag/Ab Combo (6)	99.9% (99.9%, 100%)	99.9% (99.7%, 99.9%)
GS HIV Combo Ag/Ab EIA (8)	100% (99.8%, 100%)	99.9% (99.8%, 100%)
GS HIV-1/HIV-2 Plus O EIA (5)	100% (99.8%, 100%)	99.9% (98.7%, 100%)

[a] Specificity of the Advia Centaur could not be calculated as the site using it did not submit data. Specificity of the two screening immunoassays could not be assessed in the site that switched assays as the site did not separate testing data by screening assay. One site using the ARCHITECT did not submit data required to calculate specificity.

[b] Specificity (for screening immunoassay (IA) at each submitting laboratory)= IA negative/ [IA negative +(IA false positive)] where IA false positive=number with repeatedly reactive IA, negative or indeterminate supplemental antibody test, and negative NAT. The median, minimum and maximum were calculated based on the specificity in laboratories using the specified assay.

[c] Calculated as specificity in which IA false positive= (number with repeatedly reactive IA, negative or indeterminate supplemental antibody test, and negative NAT) PLUS (number specimens eligible for NAT testing that did not receive it). The median, minimum and maximum were calculated based on the specificity in laboratories using the specified assay.

Table 3

Time from specimen collection to reporting of APTIMA (NAT) test results by the referral laboratory (n=131 specimens from 22 public health laboratories)

Process Step	Median Days (Minimum, Maximum)[a]
Specimen collection to receipt in the submitting laboratory	1 (0,13)
Receipt in the submitting laboratory to shipment to referral laboratory	6 (0,60)
Shipment	1 (1,5)
Receipt in referral laboratory to test result	2 (0,12)
Test result to reporting for specimens with reactive NAT Test result to reporting for specimens with non-reactive NAT	0 (0,1) 0 (0,3)
Total time from specimen collection to NAT result reporting, reactive NAT Total time from specimen collection to NAT result reporting, non-reactive NAT	11 (4, 63) 10 (8,19)

[a] Minimum and maximum across the public health laboratories