ORIGINAL INVESTIGATION

Detecting Acute Human Immunodeficiency Virus Infection Using 3 Different Screening Immunoassays and Nucleic Acid Amplification Testing for Human Immunodeficiency Virus RNA, 2006-2008

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Background: The yield of nucleic acid amplification testing (NAAT) after routine screening for human immunodeficiency virus (HIV) antibody to detect acute HIV infection (AHI) may vary with different HIV-antibody assays.

Methods: From April 24, 2006, through March 28, 2008, patients underwent routine HIV-antibody screening using a first-generation assay at 14 county sexually transmitted disease (STD) clinics and 1 community clinic serving homosexual patients in Los Angeles; using a second-generation rapid test at 3 municipal STD clinics in New York; and using a third-generation assay at 80 public health clinics in Florida. To identify AHI, seronegative specimens were pooled for NAAT, followed by individual NAAT of specimens with positive findings. All AHI samples screened by first- and second-generation assays also underwent third-generation testing.

Results: We screened 37 012 persons using NAAT after first-generation testing; 35 AHIs were identified, increasing HIV case detection by 8.2%. After a second-generation rapid test, 6547 persons underwent NAAT; 7 AHIs were identified, increasing HIV case detection by 24.1%. After third-generation testing, 54 948 persons underwent NAAT; 12 AHI cases were identified, increasing HIV case detection by 1.4%. Overall, pooled NAAT after negative third-generation test results detected 26 AHI cases, increasing HIV case detection by 2.2%. Most of the AHI cases from Los Angeles (26 of 35 [74%]) were identified at the community clinic where NAAT after third-generation testing increased HIV case detection by 11.9%.

Conclusions: Pooled NAAT after third-generation testing increases HIV case detection, especially in venues of high HIV seropositivity. Therefore, targeted AHI screening using pooled NAAT after third-generation testing may be most effective, warranting a cost-benefit analysis.

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Acute human immunodeficiency virus (HIV) infection (AHI) represents the stage of the disease in which viral replication and shedding occurs before detectable antibody appears.[1] During this time, viral load peaks in blood and genital secretions,[2-5] resulting in individuals who are highly infectious and are often unaware of their HIV status.[6] Individuals with AHI may have recently engaged in high-risk behaviors and have concurrent relationships.[7-16] Several models have suggested that a disproportionate number—up to 50%—of new HIV infections are acquired by onward transmission from persons with AHI.[16-21] Because most HIV-infected persons take measures to reduce their risk of further transmission after they learn of their infection,[22-25] identifying individuals during AHI affords an important opportunity for HIV prevention. Nonetheless, diagnosis of AHI is challenging and requires modification of standard HIV testing algorithms.

See also pages 6 and 57

The following 2 types of conventional HIV-antibody screening tests are approved for use in the United States: (1) first- and second-generation IgG-sensitive indirect enzyme immunoassays (EIAs) that detect antibody to viral lysate and recombinant or synthetic peptide antigens, respectively, and (2) third-generation IgM- and IgG-sensitive EIAs that use an antigen-sandwich format, increasing their ability to detect all HIV antibody isotypes.[1,26] First-generation HIV-1 EIAs are no longer available for use in the United States. Because IgM is usually expressed before IgG in response to infection, third-generation immunoassays are able to iden-

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tify persons sooner in the course of their infection compared with earlier-generation immunoassays. Because the p24 antigen, a major core HIV protein, can be detected earlier than HIV antibody, fourth-generation combination immunoassays that detect HIV antibody (IgM/IgG) and p24 antigen can identify infection even sooner than third-generation immunoassays.[26] However, fourth-generation immunoassays are not yet available in the United States.

Because conventional HIV assays test for the presence of HIV antibodies, there exists a window during which a person will have negative test results for HIV antibody despite the presence of infection[27,28] (**Figure 1**). Persons with AHI can be identified using nucleic acid amplification testing (NAAT) to detect the presence of HIV RNA during this window period.[29] Pooled NAAT, in which specimens are pooled and then tested, is a strategy that has been used routinely for blood-donor screening.[29] Nucleic acid amplification testing is predicted to detect HIV infection approximately 45 days earlier than first-generation EIAs, 32 days sooner than second-generation EIAs, 11 days sooner than third-generation EIAs, and 6 days sooner than fourth-generation EIAs[27] (Figure 1).

Several studies have shown that AHI detection using pooled NAAT after HIV-antibody screening is feasible in public health settings.[30-35] Although the yield of pooled NAAT will ultimately depend on the sensitivity during seroconversion of the screening immunoassay used,[27] all of the previous studies[30-35] examined the yield of pooled NAAT after relatively insensitive immunoassays (**Table 1**). The yield of NAAT should be lower when more sensitive screening immunoassays are used. Screening with a third- or fourth-generation assay may have detected nearly 50% to 75% of the HIV-infected persons who had negative test results of a first- or second-generation assay.[36-38] To assess the feasibility and yield of pooled NAAT relative to first-, second-, and third-generation HIV-antibody screening assays, we implemented AHI screening in 3 areas of historically high HIV prevalence in the United States. To assess the potential yield of fourth-generation screening for AHI detection, we retrospectively tested an unlinked, anonymous, blinded panel of AHI, HIV-positive and HIV-negative specimens with a fourth-generation assay that is used worldwide.

METHODS

STUDY DESIGN

We conducted an observational study to evaluate several strategies for AHI detection in Los Angeles, New York, and Florida. The primary objective was to evaluate the yield of pooled NAAT after first-, second-, and third-generation HIV-antibody screening. Additional objectives were to evaluate the yield of individual NAAT on repeatedly reactive (RR) EIA specimens, timely reporting of NAAT results and partner notification, and the sensitivity of fourth-generation assays for AHI detection.

STUDY POPULATION

From April 24, 2006, to March 28, 2008, all persons who consented to HIV testing, including NAAT, at 14 county sexually transmitted disease (STD) clinics and 1 community clinic for homosexual patients in Los Angeles, 3 health department STD clinics in New York, and approximately 80 public health clinics in 4 Florida counties participated in this study. In 2007, the prevalence of HIV was 0.6% at the Los Angeles STD clinics and 3.5% at the community clinic. In 2007, all 3 New York STD clinics had an average HIV positivity of more than 1%. In 2007, HIV positivity rates in the 4 Florida counties were 1.3% for Duval, 2.3% for Hillsborough, 2.3% for Orange, and 1.0% for Pinellas.

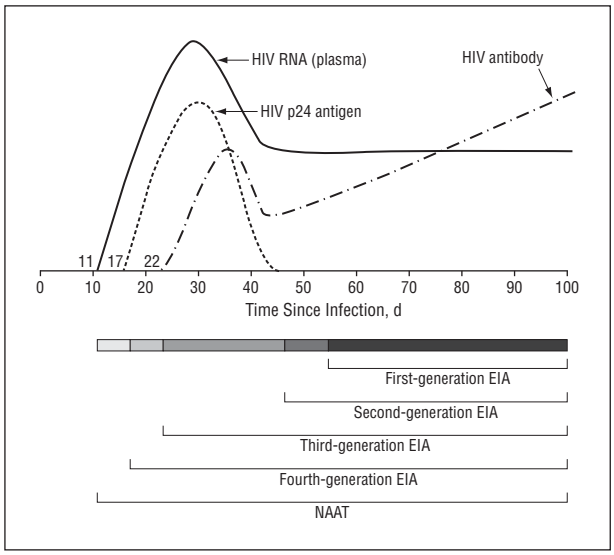

Figure 1. Window of detection of human immunodeficiency virus (HIV) markers early in HIV infection and window period of different enzyme immunoassays compared with nucleic acid amplification testing (NAAT) for HIV RNA. EIA indicates enzyme immunoassay. Data from Fiebig et al[27]; the figure was adapted from a graphic courtesy of Steven Kleinman, MD.

TESTING PROTOCOL

Plasma specimens were collected from all consenting patients at the study sites. All persons underwent initial screening for HIV antibodies; however, each project area used a different EIA. Florida used a third-generation assay (Genetic Systems HIV 1/2 Plus O; Bio-Rad Laboratories, Redmond, Washington) and, in a few study sites, a second-generation rapid test (RT) on fingerstick specimens (OraQuick; Epitope Diagnostics Inc, San Diego, California). New York used a second-generation RT (OraQuick Advance; Epitope Diagnostics Inc) on oral fluid specimens, and Los Angeles used a first-generation assay (Vironostika HIV-1 Microelisa System; bioMerieux, Inc, Durham, North Carolina). All specimens from New York and Los Angeles were subsequently tested with the third-generation assay. We did not conduct incidence testing with the BED assay or less-sensitive/more-sensitive immunoassays.

All persons who presented to study sites in Los Angeles and Florida consented to HIV screening, including NAAT, using their standard HIV testing consent forms. The New York sites used a separate consent for NAAT because persons underwent screening using an RT that provided results on the same day; the consent procedure included an explanation of the window period and AHI. Persons with negative RT results were counseled that they may still be infected with HIV if they underwent testing during the window period.

All specimens with EIA-negative findings were sent to the corresponding study laboratory for pooled NAAT using a qualitative HIV RNA assay (APTIMA HIV-1 RNA; Gen-Probe Inc, San Diego) in a 1-stage 16:1 pooling scheme (an absolute lower limit of detection of 30 copies/mL[39] permits detection of indi-

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Table 1. Summary of Studies That Have Reported Acute HIV Case Detection Using Pooled NAAT in the United States

	Source						
	Pilcher et al,[30] 2002	Pilcher et al,[31] 2005	Stekler et al,[32] 2005	Patel et al,[33] 2006	Patel et al,[33] 2006	Truong et al,[34] 2006	Priddy et al,[35] 2007
Location	North Carolina	North Carolina	Seattle, WA	San Francisco, CA	Los Angeles, CA	San Francisco, CA	Atlanta, GA
HIV antibody screening assay[a]	Vironostika HIV-1 Microelisa System	Vironostika HIV-1 Microelisa System	Vironostika HIV-1 Microelisa System	Vironostika HIV-1 Microelisa System	Vironostika HIV-1 Microelisa System	Vironostika HIV-1 Microelisa System	Genetic Systems HIV-1 rLAV
HIV antibody test generation	First	First	First	First	First	First	Second
HIV NAAT assay	Roche Ultrasensitive[b]	Roche Ultrasensitive[b]	GenProbe Procleix[c]	Bayer Versant bDNA[d]	Roche Ultrasensitive[b]	Bayer Versant bDNA[d]	GenProbe Procleix[c]
Pool size	100	100	30	50/10[e]	90	10	48
No. of HIV antibody-negative specimens screened	8155	108 667	3439	2969	1712	3664	2127
No. of prevalent HIV-positive specimens	39	583	81	105	14	125	66
Acute cases, No. (%)	4 (0.05)	23 (0.02)	7 (0.2)	11 (0.4)	1 (0.1)	11 (0.3)	4 (0.2)
Increase in HIV case detection, %	10.3	3.9	8.6	10.5	7.1	8.1	5.7

Abbreviations: HIV, human immunodeficiency virus; NAAT, nucleic acid amplification testing.
[a] Proprietary information is given in the "Testing Protocol" subsection of the "Methods" section.
[b] From Roche Molecular Systems, Indianapolis, Indiana.
[c] From Chiron Corporation, Emeryville, California.
[d] From Bayer Corporation, Tarrytown, New York.
[e] Study initially tested specimens in pools of 50 and then switched to pools of 10 for faster turnaround of NAAT results.

vidual specimens with ≥1070 copies/mL in a master pool with 1:16 dilution[40]). The specimens from Los Angeles and New York underwent testing at the Wadsworth Center of the New York State Department of Health, and specimens from Florida were tested at the Florida Bureau of Laboratories. All pools with NAAT-positive results underwent retesting and, if results were repeatedly positive, the pool was deconstructed and each individual specimen underwent NAAT. All individual specimens with NAAT-positive findings underwent retesting in duplicate and confirmation with viral load quantification (Versant HIV-1 RNA 3.0 assay; Siemens Healthcare Diagnostics, Malvern, Pennsylvania) before they were reported to study sites as being NAAT positive. All specimens with EIA-RR/Western blot (WB)–indeterminate and EIA-RR/WB-negative results were tested with NAAT individually; those with NAAT-positive results were confirmed with viral load quantification (**Figure 2**). If the viral load was undetectable, follow-up testing was conducted to resolve the discrepant test results.

AHI CASE DEFINITION

Based on the initial screening results, all persons with EIA-negative/NAAT-positive results, EIA-RR/WB-indeterminate/NAAT-positive results, and EIA-RR/WB-negative/NAAT-positive results and who had detectable viral loads were considered presumptive AHI cases; we included persons with WB-negative or -indeterminate results in our case definition because they were most likely in the window period. Persons with presumptive AHI had specimens drawn for follow-up confirmatory testing on the day they received their test results. Follow-up plasma specimens underwent EIA, WB, individual NAAT, and viral load testing. After this second confirmatory test, patients with NAAT-positive results who continued to have negative or indeterminate WB results were followed up every 2 weeks for up to 12 weeks to confirm HIV seroconversion.

We obtained demographic and risk-factor data on all persons who consented to HIV testing from routinely collected, program-specific HIV counseling and testing forms.

FIELD PROTOCOL

Disease intervention specialists, public health workers who are responsible for finding and counseling people with STDs and their contacts, were specially trained to notify presumptive AHI cases of their results and the need for confirmatory testing and to refer persons to care and partner notification services. Sexual or needle-sharing partners of AHI cases were notified as soon as possible and offered HIV testing using the same study protocol. We did not collect information about postexposure prophylaxis.

EVALUATION OF FOURTH-GENERATION ASSAY

To evaluate fourth-generation screening for AHI detection, an unlinked, anonymous, blinded panel of 38 AHI, 43 HIV-positive, and 119 HIV-negative specimens was sent to Abbott Diagnostics, Abbott Park, Illinois, for testing with the Architect HIV Ag/Ab Combo assay (List 4J27; Abbott Diagnostics, Wiesbaden, Germany; available for sale outside the United States only). The 38 AHI specimens were from persons with documented seroconversion and included initial and follow-up specimens from the same individual. Because this assay is not approved by the US Food and Drug Administration, this evaluation was conducted retrospectively and results were not reported to participants; however, it was expected that fourth-generation assay results would not alter the interpretation of participants' HIV test results.

ANALYSIS

Presumptive AHI was defined as in the "AHI Case Definition" subsection. Persons with EIA-RR/WB-positive results, regard-

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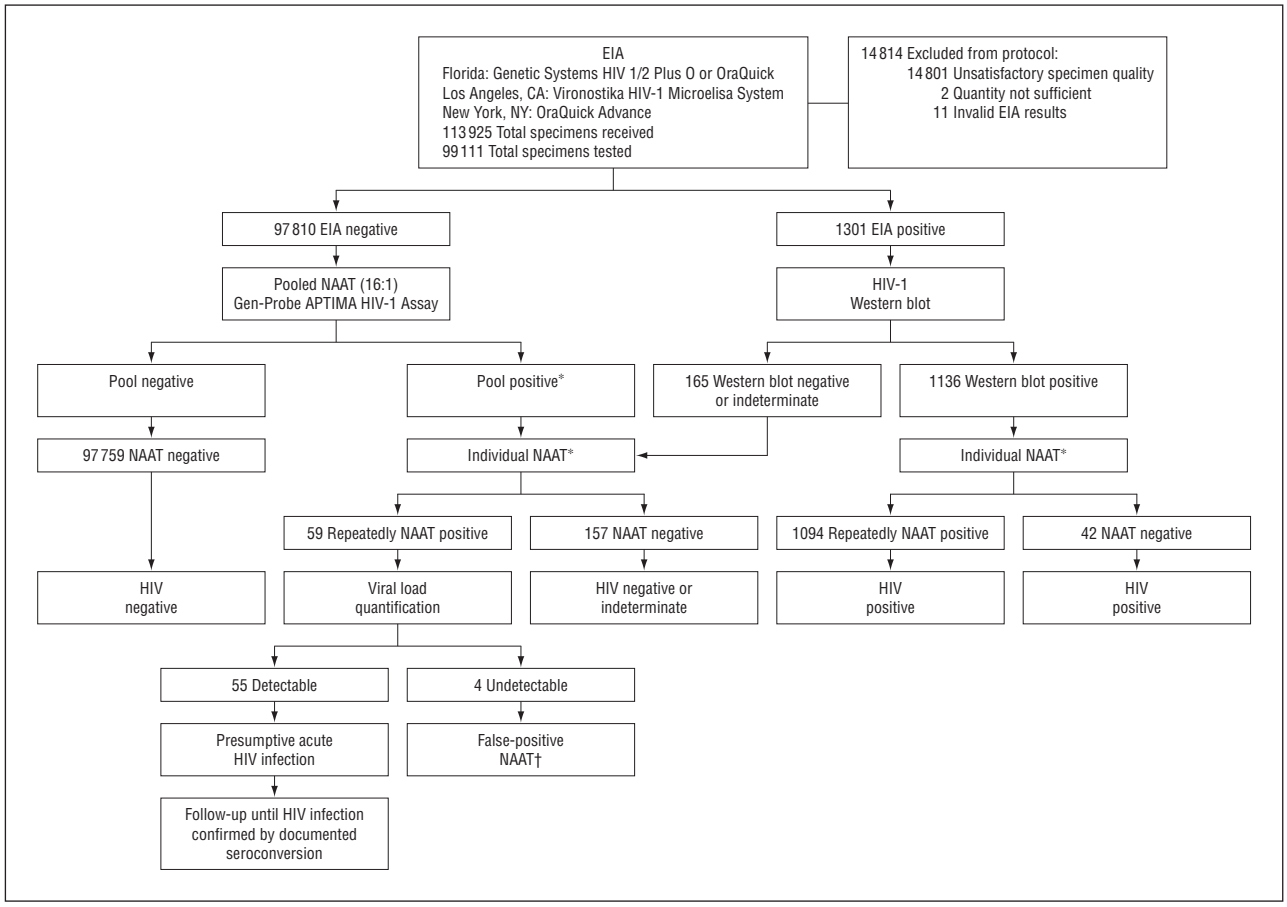

Figure 2. Human immunodeficiency virus (HIV) screening algorithm with pooled nucleic acid amplification testing (NAAT) for the Centers for Disease Control and Prevention Acute HIV Infection Study, 2006-2008. EIA indicates enzyme immunoassay. The proprietary information on the EIAs and APTIMA HIV-1 Assay is given in the "Testing Protocol" subsection of the "Methods" section. *Positive pools and individual specimens underwent testing in duplicate for suspected acute/primary HIV infection.[39] †Persons with specimens with positive NAAT results but an undetectable viral load underwent follow-up testing to resolve discrepant results.

less of the NAAT result, were considered established cases of HIV infection. For each and all project areas combined, we report the number and percentage of specimens that were received for screening, specimens undergoing testing with NAAT, persons with presumptive AHI, and persons with AHI with documented seroconversion. In addition, we calculated the increase in HIV case detection attributed to NAAT. Descriptive and univariate analyses were conducted using commercially available software (SAS, version 9.2; SAS Institute Inc, Cary, North Carolina). Test performance characteristics, such as specificity, were calculated using an open-source software program (OpenEpi, version 2.2.1; Emory Rollins School of Public Health).[41-43]

HUMAN SUBJECTS PROTECTIONS

The Centers for Disease Control and Prevention (CDC) and local institutional review board approvals were obtained by all 3 project areas. The evaluation of the fourth-generation assay was granted a nonresearch determination per CDC guidelines.

RESULTS

STUDY POPULATION

From April 24, 2006, through March 28, 2008, 99 111 persons underwent testing using an antibody plus NAAT algorithm (Figure 2) in Los Angeles, New York, and Florida. Of all 99 111 persons who underwent screening, the median age was 26 (range, 14-111) years; 52.0% were female, 37.4% were black non-Hispanic, and 68.3% were self-identified heterosexuals. Of the 9832 participants who identified themselves as men who have sex with men, 71.3% underwent screening in Los Angeles (**Table 2**).

CASE IDENTIFICATION

In Los Angeles, from May 1, 2006, through February 29, 2008, 37 012 specimens were screened for HIV. Of these, 36 512 (98.6%) had EIA-negative/NAAT-negative results, and 424 (1.1%) had EIA-RR/WB-positive results. Of 36 individuals who met the AHI case definition, 1 had a false-positive NAAT result. Adding NAAT to first-generation EIA screening in Los Angeles increased HIV case detection by 8.2%. Of the 35 persons with AHI, 17 (48.6%) were detected with the third-generation assay, decreasing the yield of NAAT to 4.1% (**Table 3**).

Twenty-six of the Los Angeles AHI cases (74%) were identified at the community clinic. Of 5863 specimens screened at the community clinic, 105 (1.8%) had EIA-RR/WB-positive/NAAT-positive results, and 26 (0.4%) met the AHI case definition. Adding NAAT to first-generation

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Table 2. Characteristics of CDC Acute HIV Infection Study Population and Project Areas, 2006-2008[a]

Characteristic	Los Angeles, CA[b] (n=37 012)	New York, NY[c] (n=6547)	Florida[d] (n=55 552)
Study population			
Age, range, y			
≤17	577 (1.6)	49 (0.7)	10 777 (19.4)
18-20	2399 (6.5)	942 (14.4)	26 110 (47.0)
21-30	14 426 (39.0)	3316 (50.6)	10 499 (18.9)
31-40	7818 (21.1)	1279 (19.5)	5166 (9.3)
41-50	4977 (13.4)	696 (10.6)	1722 (3.1)
51-60	1761 (4.8)	202 (3.1)	722 (1.3)
≥61	750 (2.0)	63 (1.0)	556 (1.0)
Unknown	4304 (11.6)	0	0
Sex			
Male	23 524 (63.6)	3764 (57.5)	16 499 (29.7)
Female	10 810 (29.2)	2780 (42.5)	37 942 (68.3)
Transgender	107 (0.3)	3 (0.05)	0
Unknown	2571 (6.9)	0	1111 (2.0)
Race[e]			
White, non-Hispanic	6951 (18.8)	752 (11.5)	11 890 (21.4)
Black, non-Hispanic	11 747 (31.7)	3366 (51.4)	21 969 (39.5)
Hispanic	13 100 (35.4)	2079 (31.8)	13 844 (24.9)
Hawaiian/Pacific Islander	98 (0.3)	9 (0.1)	222 (0.4)
Asian	1636 (4.4)	109 (1.7)	889 (1.6)
American Indian/Alaskan	106 (0.3)	19 (0.3)	167 (0.3)
Other	781 (2.1)	213 (3.3)	0
Refused/unknown	2593 (7.0)	0	6571 (11.7)
Risk for HIV infection			
Male-male sex, including IDU	7007 (18.9)	658 (10.1)	2167 (3.9)
IDU	155 (0.4)	0	1167 (2.1)
Male-female sex	26 357 (71.2)	5761 (88.0)	35 553 (64.0)
Other risks[f]	532 (1.4)	128 (2.0)	16 665 (30.0)
No identified risk/unknown	2961 (8.0)	0	0

(*continued*)

Table 2. Characteristics of CDC Acute HIV Infection Study Population and Project Areas, 2006-2008[a] (continued)

Characteristic	Los Angeles, CA[b] (n=37 012)	New York, NY[c] (n=6547)	Florida[d] (n=55 552)
Characteristics of project area			
AIDS prevalence in 2006[g] per 100 000 persons	14.4	40.8	27.3
Modal race/ethnicity risk group for AIDS diagnoses in 2006	White MSM	Black/ Hispanic MSM	Black heterosexuals
HIV screening assay[h]	Vironostika HIV-1 Microelisa System	OraQuick Advance	Genetic Systems HIV 1/2 Plus 0 or OraQuick
Specimen type	Venipuncture	Oral fluid	Venipuncture or fingerstick
HIV antibody test generation	First	Second	Third or second
Type of test sites	STD clinics + community center for homosexual patients	STD clinics	Public health clinics
Pooled NAAT laboratory	New York State	New York State	Florida
NAAT study period	May 2006 to February 2008	June 2007 to March 2008	April 2006 to February 2008

Abbreviations: CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; IDU, injected drug use; MSM, male-male sexual intercourse; NAAT, nucleic acid amplification testing; STD, sexually transmitted disease.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients. All percentages have been rounded and thus may not add to 100.

[b] Specimens were received from the following 8 service planning areas: Antelope Valley, San Fernando, San Gabriel, West, Metro, South, East, and South Bay.

[c] Specimens were received from the following 3 boroughs: Bronx, Brooklyn, and Manhattan.

[d] Specimens were received from the following 4 counties: Duval, Hillsborough, Orange, and Pinellas.

[e] Race categories are mutually exclusive.

[f] Include hemophilic/transfusion recipient, history of incarceration, needle sharing with partner of unknown HIV status, sex with an HIV-positive partner, sex with anonymous partners, sex for drugs, sex with an incarcerated person, and sex with an intravenous drug user.

[g] Indicates estimated AIDS prevalence in 2006 from HIV/AIDS surveillance report.[44]

[h] Proprietary information is found in the "Testing Protocol" subsection of the "Methods" section.

EIA screening at the community clinic increased HIV case detection by 24.7%. Of the 26 persons with AHI, 12 (46%) were detected with the third-generation assay, decreasing the yield of NAAT to 11.9%.

The other 9 persons with AHI were identified at the Los Angeles STD clinics, where NAAT after first-generation screening increased HIV case detection by 2.8%. Five of the AHI cases were detected with the third-generation assay, decreasing the yield of NAAT to 1.5%.

In New York, from June 1, 2007, through March 28, 2008, 6547 specimens underwent screening for HIV. Of these, 6481 (99.0%) had RT-negative/NAAT-negative findings, and 29 (0.4%) had RT-positive/WB-positive/NAAT-positive findings. Seven individuals (0.1%) had test results that met the AHI case definition. Adding NAAT to second-generation RT screening in New York increased HIV case detection by 24.1%. Of the 7 persons with AHI, the infection was detected in 6 (85.7%) with the third-generation assay, decreasing the yield of NAAT to 2.9% (Table 3).

In Florida, from April 1, 2006, to February 29, 2008, 54 948 specimens underwent screening for HIV. Of these, 54 180 (98.6%) had EIA-negative/NAAT-negative results, and 663 (1.2%) had EIA-RR/WB-positive results. Fifteen individuals had test results that met the AHI case definition, of whom 3 had false-positive NAAT results. Of the 12 persons with AHI, 7 had EIA-negative/NAAT-positive results, 2 had EIA-RR/WB-negative/NAAT-positive results, and 3 had EIA-RR/WB-indeterminate/NAAT-positive results. Adding NAAT to third-generation EIA screening in Florida increased HIV case detection by 1.4% (Table 3).

In Florida, from September 1, 2007, through February 29, 2008, 604 specimens were received from RT sites, of

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Table 3. CDC Acute HIV Infection Study Results by Project Area, 2006-2008[a]

Characteristic	Study Site (Antibody Test Generation)			
	Los Angeles, CA (First)	New York, NY (Second)	Florida (Third)	Florida (Second)
Total No. of specimens tested	37 012	6547	54 948	604
HIV– results	36 539 (98.7)	6511 (99.5)	54 253 (98.7)	586 (97.0)
EIA–/NAAT–	36 512 (98.6)	6481 (99.0)	54 180 (98.6)	586 (97.0)
EIA-RR/WB–/NAAT–	27 (0.1)	30 (0.5)	73 (0.1)	0
HIV+ results	427 (1.2)	29 (0.4)	663 (1.2)	17 (2.8)
EIA-RR/WB+/NAAT+	424 (1.1)	29 (0.4)	624 (1.1)	17 (2.8)
EIA-RR/WB+/NAAT–	3 (0.01)	0	39 (0.1)	0
HIV-indeterminate results				
EIA-RR/WB-indeterminate/NAAT–	10 (0.03)	0	17 (0.03)	0
Presumptive AHI				
EIA–/NAAT+	35 (0.1)	7 (0.1)	7 (0.01)	1 (0.2)
EIA-RR/WB–/NAAT+	0	0	2 (0.004)	0
EIA-RR/WB-indeterminate/NAAT+	0	0	3 (0.01)	0
Total No. of unique AHI cases[b]	35 (0.1)	7 (0.1)	12 (0.02)	1 (0.2)
AHI cases with documented seroconversion	30 (0.1)	6 (0.1)	11 (0.02)	1 (0.2)
Presumptive AHI cases that were lost to follow-up	5 (0.01)	1 (0.02)	1 (0.002)	0
Total No. of documented false-positive NAAT results	1 (0.003)	0	3 (0.01)	0
Increase in HIV case detection with NAAT, %	8.2	24.1[c]	1.4	5.9
No. of AHIs detected with third-generation EIA	17 (48.6)	6 (85.7)	NA	0
Increase in HIV case detection with third-generation EIA, %	4.0	20.7	NA	0
Increase in HIV case detection with NAAT after third-generation EIA, %	4.1	2.9	1.4	5.9
No. of AHIs tested with fourth-generation Ab/Ag assay	14 (40.0)	3 (42.9)	11 (91.7)	1 (100)
No. of AHIs detected with fourth-generation Ab/Ag assay	12 (85.7)	3 (100)	9 (81.8)	1 (100)
Increase in HIV case detection with NAAT after fourth-generation Ab/Ag assay, %[d]	1.0	0	0.3	0

Abbreviations: Ab/Ag, human immunodeficiency virus (HIV) antibody/p24 antigen; AHI, acute HIV infection; EIA, enzyme immunoassay; NA, not applicable; RR, repeatedly reactive; WB, Western blot; – negative; + positive. See Table 2 for other definitions.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.

[b] Percentage is of total number of specimens undergoing testing.

[c] Increase in case detection is based on a subset of the entire testing population because New York implemented a separate consent for AHI screening with NAAT.

[d] Used an estimated proportion of the total number of AHIs detected by the fourth-generation assay based on actual testing.

which 586 (97.0%) had negative RT results (OraQuick) and 17 (2.8%) had positive results confirmed by WB. One individual had test results that met the AHI case definition. This AHI case had a negative third-generation test result (Table 3). Adding NAAT to second-generation RT screening in Florida increased HIV case detection by 5.9%.

Of all 99 111 specimens undergoing testing for HIV in all 3 project areas, 97 908 (98.8%) had negative results with the third-generation assay and 1160 (1.2%) had positive results. Twenty-six individuals had NAAT-positive results and were considered AHI cases. Therefore, pooled NAAT after negative third-generation test results increased HIV case detection by 2.2% (range by site: 1.4%-5.9%) (Table 3).

CASE AND PARTNER NOTIFICATION

Of the 55 persons identified with AHI, 48 (87%) received their NAAT result and 7 were lost to follow-up; 12 of the 55 (22%) reported a recent known exposure to HIV. Of the 48 persons who received their results, 11 (23%) received their results within 7 days of testing; 23 (48%), within 8 to 14 days of testing; and 14 (29%), more than 14 days after testing (**Table 4**). The Florida sites had the longest turnaround time of reporting NAAT results to persons with AHI. We experienced courier-related shipping delays in Los Angeles and Florida that rendered many specimens unsatisfactory for testing. To increase specimen integrity, we switched from EDTA to plasma preparation tubes that required centrifugation. Also, Los Angeles specimens were shipped across the country to New York for NAAT after the Los Angeles public health laboratory performed initial HIV-antibody screening. Therefore, Los Angeles had the longest turnaround time of NAAT results from the laboratory to the health department (Table 4).

Of the 48 persons with AHI who received their results, all accepted partner notification services. These persons named 72 partners; 23 of these (32%) underwent testing, of whom 5 (21.7%) were found to be HIV-positive. Two partners were pregnant women, both of whom had HIV-negative results.

PERFORMANCE OF POOLED NAAT

Of the 59 persons with presumptive AHI, 48 had documented seroconversion based on follow-up testing, and 7 were lost to follow-up. Four persons with presumptive AHI had negative NAAT results and an undetectable viral load on follow-up testing and were classified as false-positive cases. The distribution of the initial test results of the 4 false-positive cases included 1 EIA-negative/NAAT-positive result, 2 EIA-RR/WB-negative/NAAT-positive results, and 1 EIA-RR/WB-indeterminate/NAAT-positive result. All 55 persons with AHI had a

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Table 4. NAAT Results Reporting and Partner Notification Outcomes, CDC Acute HIV Infection Study by Project Area, 2006-2008

Characteristic	Study Center		
	Los Angeles, CA (n=35)	New York, NY (n=7)	Florida (n=13)
Timeliness of NAAT result reporting to health department			
Time for laboratory turnaround of NAAT result, median (range), d	6 (3-10)	3 (2-8)	4 (3-6)
Timeliness of NAAT result reporting to client, No. (%)			
Time until NAAT results reported to client, d			
≤7	5 (14)	6 (86)	0
8-14	18 (51)	1 (14)	4 (31)
>14	6 (17)	0	8 (62)
Client lost to follow-up	6 (17)	0	1 (8)
Total No. informed of NAAT result	29 (83)	7 (100)	12 (92)
Time for health department to report NAAT result, median (range), d	11 (3-51)	7 (6-8)	17 (10-107)
Provision of partner notification			
Partner notification accepted, No. (%)	29 (83)	7 (100)	12 (92)
Client lost to follow-up, No. (%)	6 (17)	0	1 (8)
No. of partners named	23	25	24
No. of partners tested	5	6	12
No. of partners with HIV-positive test results	1	1	3

Abbreviations: CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; NAAT, nucleic acid amplification testing.

detectable viral load (median, 310 975 [range, 92-6 334 400] copies/mL). Overall, the positive predictive value of pooled NAAT for identifying AHI among antibody-negative specimens was 0.9804 (95% confidence interval [CI], 0.9071-0.9990) with a specificity of 0.9998 (95% CI, 0.9992-1.000). Sensitivity cannot be estimated because the NAAT-negative pools were not deconstructed and confirmed negative. Forty-two persons with EIA-RR/WB-positive results had NAAT-negative results (Table 3); 28 of these persons (67%) were known to be seropositive, with a history of antiretroviral use.

PERFORMANCE OF FOURTH-GENERATION TESTING

Of the 55 persons with AHI, 27 had enough plasma for fourth-generation testing, and 23 of these (85%) had positive findings. The fourth-generation assay detected 10 of 13 AHI cases (77%) that were missed by the third-generation assay. The 4 AHI specimens with negative fourth-generation assay results also had negative third-generation assay results. These 4 cases had a median viral load of 6961 (range, 1827-21 548) copies/mL. Pooled NAAT after negative fourth-generation testing may have increased HIV case detection by only 0.7%. Furthermore, fourth-generation testing of the blinded specimen panel resulted in 2 false-positive and 4 false-negative results. Therefore, the sensitivity of the Architect HIV Ag/Ab Combo assay compared with NAAT was 0.9506 (95% CI, 0.8852-0.9841), and specificity was 0.9834 (95% CI, 0.9456-0.9972).

COMMENT

This is, to our knowledge, the first study to compare the yield of NAAT after screening with different antibody tests. Our data suggest that pooled NAAT increases HIV case detection most when used with less sensitive screening immunoassays.[31-36] However, the third-generation EIA was able to detect HIV infection in 50.9% of all AHI cases identified in this study. Thus, pooled NAAT after screening with a third-generation EIA increased our HIV case detection by 2.2% overall. The marginal yield of pooled NAAT after third-generation testing, however, may be even more substantial in targeted screening of high-risk persons. In Los Angeles, pooled NAAT after third-generation testing resulted in the highest increase in HIV case detection at the community center (11.9%), where HIV positivity was the highest. This suggests that targeted AHI screening at high-risk/high-incidence venues using pooled NAAT may be most effective.

According to the Association of Public Health Laboratories survey,[45] of all laboratories surveyed in 2006, most (58%) were using a first-generation assay that is no longer available today. Given our study results, public health laboratories should consider using the most sensitive EIA available for HIV screening, which currently is a third-generation assay, in the absence of NAAT for antibody-negative specimens. Although only half of the AHI cases underwent retrospective fourth-generation testing, 85.1% of those tested were detected. These data suggest that pooled NAAT after negative fourth-generation testing may increase HIV case detection by only 0.7%. Although fourth-generation assays are the preferred test for HIV screening among routine testing populations in other countries, none are available for use in the United States. The marginal yield (0.7%) of NAAT after fourth-generation testing in our study was similar to findings (1.1%) reported in Australia.[37] The AHI cases missed by fourth-generation testing had low viral loads, suggesting early acute-phase infection. Hence, the yield of pooled NAAT after fourth-generation testing may be maximized in high-incidence populations where early AHI cases are most probable. Further evaluation of NAAT after fourth-generation testing in high-risk/high-incidence settings is warranted.

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Detection of AHI can only realize its full HIV prevention potential with timely reporting of results and partner notification. In our study, 48 AHI cases (87%) received their results and accepted partner notification services; only 11 (23%) received their results within 7 days and only 23 of the named partners (32%) underwent testing. To interrupt further transmission, persons with AHI should be located immediately, preferably within 72 hours of testing, and their sexual contacts should be urgently located and undergo testing.[46,47] Studies have shown that partners of HIV-positive persons who accept partner notification services have rates of HIV positivity as high as 57%.[48-50] However, many local health departments, including our study sites, have limited capacity and insufficient funding for their partner notification programs and are therefore able to locate only a small number of partners in a timely manner. To maximize HIV screening services (with or without NAAT), partner notification programs should be strengthened so that they have a better capacity to find at-risk partners and use novel and innovative strategies[51-53] to locate and test persons quickly to preclude further HIV transmission.

Our study had several limitations. First, we implemented the study differently in each project area to accommodate existing program procedures, which limited our ability to compare all outcomes across project areas. Specifically, New York implemented a separate consent for NAAT, which led to client self-selection for NAAT. As a result, our findings might overestimate the yield of NAAT in New York if clients were more likely to opt for AHI screening because of recent high-risk behaviors. Second, shipping delays increased the turnaround time for reporting results in Los Angeles. Third, we did not conduct a real-time evaluation of fourth-generation assays because they are not currently available in the United States, and we tested a small subset of specimens, which may have introduced a potential bias. Finally, NAAT may miss persons with long-standing HIV infection; we had 42 false-negative NAAT results (Figure 2). Moreover, there is an eclipse phase of 10 to 11 days after initial HIV infection during which HIV viremia is undetectable.[27] Given that the length of the eclipse phase is similar to the window period with third-generation assays, the number of infections missed by NAAT during this phase may be equal to the number of AHIs detected among seronegative persons. Thus, particularly in high-incidence sites like the Los Angeles community clinic, patients should be encouraged to undergo retesting, especially after a risk exposure, consistent with current CDC recommendations.[44]

Adding NAAT to HIV screening programs adds cost because pooled NAAT is feasible only after antibody testing (both must be performed). However, the cost of NAAT reported from previous studies has varied with the number of persons with AHIs identified.[30,31,33] Furthermore, although NAAT is more expensive than immunoassays, the fourth-generation immunoassay cannot distinguish between acute and prevalent HIV infection; this would require supplemental testing, adding to cost. Therefore, formal cost and cost-effectiveness analyses are under way.

Screening for AHI can maximize HIV case detection. However, implementing strategies to distinguish AHI from prevalent HIV infection maximizes prevention benefits only if programs are able to (1) provide referral for appropriate clinical management, (2) conduct urgent partner notification and testing, and (3) investigate foci or networks of HIV transmission. Our study supports AHI screening with pooled NAAT after third-generation assays in areas of high HIV prevalence. Therefore, targeted AHI screening using pooled NAAT after third-generation testing may be most effective. Further studies of AHI screening with new testing technologies among high-risk/high-incidence populations are warranted. Finally, when fourth-generation assays become available in the United States, it is less clear whether NAAT should play a role in AHI screening programs.

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