



Revisiting Expectations from Rapid HIV Tests and Confirmation Algorithms in the Emergency Department

Rochelle P. Walensky, Christian Arbelaez, William M. Reichmann, Ron M. Walls, Jeffrey N. Katz, Brian Block, Matthew Dooley, Adam Hetland, Simeon Kimmel, Jessica Solomon, Elena Losina

Massachusetts General Hospital, Brigham and Women's Hospital, Harvard Medical School, Boston University School of Public Health, Boston, MA,

Supported by the National Institute of Mental Health (R01 MH073445, R01 MH65869), and the Doris Duke Charitable Foundation (Clinical Scientist Development Award)

Rochelle Walensky, MD, MPH
 Division of General Medicine
 Massachusetts General Hospital
 50 Stanfords Street, 9th Floor
 Boston, MA 02114
 rwalensky@partners.org
 Tel: 617-724-3467
 Fax: 617-726-2691

BACKGROUND

- Rapid HIV tests are becoming more widely used to scale up routine HIV screening in the U.S.
- Even a highly accurate test may generate preliminary reactive test results in the absence of disease, especially at a low prevalence of HIV infection.
- Providers must be appropriately trained to assist in the interpretation and adequate follow-up of reactive rapid test results.

OBJECTIVE

- To evaluate the performance of a rapid HIV test in the context of an HIV screening study in an urban tertiary care emergency department (ED) setting.

METHODS

- Site and Eligibility**
- The Brigham and Women's Hospital Emergency Department (BWH ED) is a tertiary referral center in Boston.
 - Eligible patients were:
 - 18-75 y/o
 - Of clear mental status; ESI score ≥ 3
 - Fluent in English or Spanish
 - Not known to be HIV-infected

- Screening Instrument**
- OraQuick® ADVANCE™ Rapid HIV-1/2 Antibody Test (oral)

- Confirmation Protocol**
- All patients with reactive OraQuick® tests were offered confirmatory testing with: serum HIV EIA and Western Blot, CD4 cell count, and HIV RNA testing
 - Confirmation required an additional informed consent

- Test Performance**
- We evaluated the specificity of the rapid HIV test using the confirmatory tests as a gold standard, the likelihood ratio positive, the overall positive predictive value (PPV), the PPV stratified by intensity of the reactive line compared to positive controls provided by the manufacturer.

RESULTS

- From 2/1/07-10/1/07, 2,620 patients were offered enrollment
- 849 patients were tested with reportable test results.
- 39 patients had reactive OraQuick® test results (4.6%, 95% CI 3.2-6.0%).
- 31/39 patients agreed to confirmatory testing.
- 5/31 patients confirmed HIV infected (HIV prevalence 0.6%, 95% CI 0.1-1.1%).
- 13/26 (50%, 95% CI 30.8%, 69.2%) of HIV-uninfected patients had indeterminate Western Blots (HIV RNA was undetectable).

Table 1: Demographic Characteristics of patients HIV-tested in the USHER Trial*

| | Reactive Test N=39 n (%) | Non-Reactive Test N=810 n (%) | p-value |
|---------------------------|--------------------------------|-------------------------------------|---------|
| Mean Age (yrs, SD) | 46.0 (13.7) | 37.0 (14.2) | <0.01 |
| Male | 18 (46.2%) | 286 (35.6%) | 0.18 |
| Race | | | 0.62 |
| Caucasian | 14 (36.8%) | 320 (40.9%) | |
| African American | 10 (26.3%) | 155 (19.8%) | |
| Other | 14 (36.8%) | 308 (39.3%) | |
| Ethnicity | | | 0.86 |
| Hispanic | 12 (30.8%) | 260 (32.1%) | |
| Non-Hispanic | 27 (69.2%) | 550 (67.9%) | |
| Primary Language | | | 0.93 |
| English | 29 (74.4%) | 585 (72.2%) | |
| Spanish | 8 (20.5%) | 172 (21.2%) | |
| Other | 2 (5.1%) | 53 (6.5%) | |

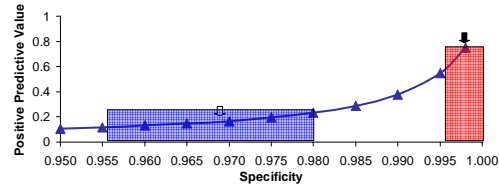
*1 patient with a reactive test had missing data for race; among patients with non-reactive tests, 3 did not report age, 7 did not report gender and 27 did not report race.

TEST PERFORMANCE

- Specificity** = 96.9% (95% CI 95.7%-98.1%). This is statistically significantly lower than the manufacturer reported specificity of 99.8% (95% CI 99.6-99.9%)
- Likelihood Ratio Positive** (sensitivity/[1-specificity]) = 32.1
- Positive Predictive Value** (at 0.6% prevalence) = 16.1% (95% CI 3.2-29.1%)

RESULTS

Figure 1: Positive predictive value as a function of specificity and HIV prevalence



- Red-shaded area provides the 95% CI of the manufacturer reported specificity.
- Blue-shaded area provides the 95% CI of the specificity in this study
- Hollow arrow provides the PPV achieved in this study (16.1%)
- Solid arrow provides the PPV that would have been achieved had the test operated at the manufacturer reported specificity (75.0%)

Table 2: Confirmatory results and positive predictive value among those who confirmed and had faintness of the line documented (n=23).

| | HIV + | Positive Predictive Value | 95% Confidence Interval |
|-------------------|-------|---------------------------|-------------------------|
| Faint Line (n=19) | 0 | 0% | 0-16.0% |
| Dark Line (n=4) | 4 | 100% | 45.0-100% |

DISCUSSION

- The newly identified HIV prevalence of 0.6% is in compliance with the CDC routine screening guidelines.
- HIV testing should continue at this site.

Specificity and Positive Predictive Value

- Figure 1 highlights the important interplay between HIV prevalence, specificity and PPV. At low prevalences (<1%), small leftward shifts in specificity result in large changes in positive predictive value (75% vs. 16%).
- While other studies have previously reported oral rapid HIV tests with lower than expected specificity (NYC, LA, SF, Minneapolis and Washington DC), many programs do not report specificity, false positives or confirmation protocols.
- To evaluate the scope of this issue, testing programs should implement a reporting standard that includes: type of test (means of specimen collection), confirmation protocol, and rate of false positive results.
- Even at a PPV of 16%, rapid HIV testing functions better than many other screening tests in US practice (e.g. mammography PPV = 9%)

Stratifying the Results by Reactive Line Intensity

- These results suggest that the PPV improves substantially when reactive results are stratified by lines that are "darker" or "fainter" than positive controls.
- To conclude that all faint lines are non-reactive might misclassify patients as being uninfected when they really have HIV. Patients with faint lines should be offered confirmation, with acknowledgement that their results are reactive but suggestive of HIV negativity.

Confirmation Protocols

- 50% (13/26) of patients with reactive rapid tests and who were HIV negative by HIV RNA had indeterminate Western Blots.
- In the absence of HIV RNA data, these patients' screening and confirmatory results might suggest early HIV infection.
- The addition of serum EIA and HIV RNA level to the confirmation protocol provided a conclusive uninfected HIV status in 96.2% of patients at first follow-up.
- HIV RNA testing should be added to the rapid test confirmatory protocol.

CONCLUSIONS

- The results of this study support the original intent of the HIV screening guidelines – to identify undiagnosed HIV infection.
- Oral sampling using the OraQuick® HIV screening test in the emergency department may perform at lower specificity and positive predictive value than initially anticipated.
- Performance characteristics improve substantially when results are stratified according to the darkness of the reactive line.
- Confirmatory algorithms should include HIV RNA testing to improve the capacity to deliver conclusive results at first follow-up.