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## False-Positive Oral Fluid Rapid HIV Tests — New York City, 2005–2008

The New York City Department of Health and Mental Hygiene (NYC DOHMH) operates 10 sexually transmitted disease (STD) walk-in clinics offering various free services, including confidential or anonymous testing for human immunodeficiency virus (HIV). In January 2004, the STD clinics introduced on-site rapid HIV testing of finger-stick whole-blood specimens using the OraQuick<sup>®</sup> brand test (OraSure Technologies, Bethlehem, Pennsylvania). In March 2005, the clinics replaced finger-stick whole-blood testing with oral fluid testing with the OraQuick Advance Rapid HIV-1/2 Antibody Test.\* The clinics use Western blot confirmatory tests on serum to confirm all whole-blood or oral fluid reactive (i.e., preliminary positive) rapid tests. In late 2005, an unexpected increase in the number of false-positive oral fluid tests occurred, but the increase subsided after several months. In December 2005, while the cluster of false-positive oral fluid test results was being investigated, the NYC DOHMH Bureau of STD Control suspended oral fluid testing in the clinics for 3 weeks and replaced it with finger-stick whole-blood rapid testing, which produced no false-positive test results. On December 21, 2005, NYC DOHMH resumed oral fluid rapid testing but also introduced the use of immediate follow-up finger-stick whole-blood testing, using a second OraQuick test, after any reactive oral fluid test result. In late 2007, another larger increase in the incidence of false-positive oral fluid rapid test results was observed. The cause for the episodic increases in false-positive oral fluid tests has not yet been determined. NYC DOHMH has again suspended the use of oral fluid testing in STD clinics, and finger-stick whole-blood testing is the only rapid HIV test being used in this setting. These findings underscore the importance of confirming all reactive HIV tests, both from oral fluid and whole-blood specimens. In addition, the results suggest that the NYC DOHMH strategy of following up reactive oral fluid test results with an immediate finger-stick whole-blood test reduced the number of apparent false-positive oral fluid test results and might be a useful strategy in other settings and locations.

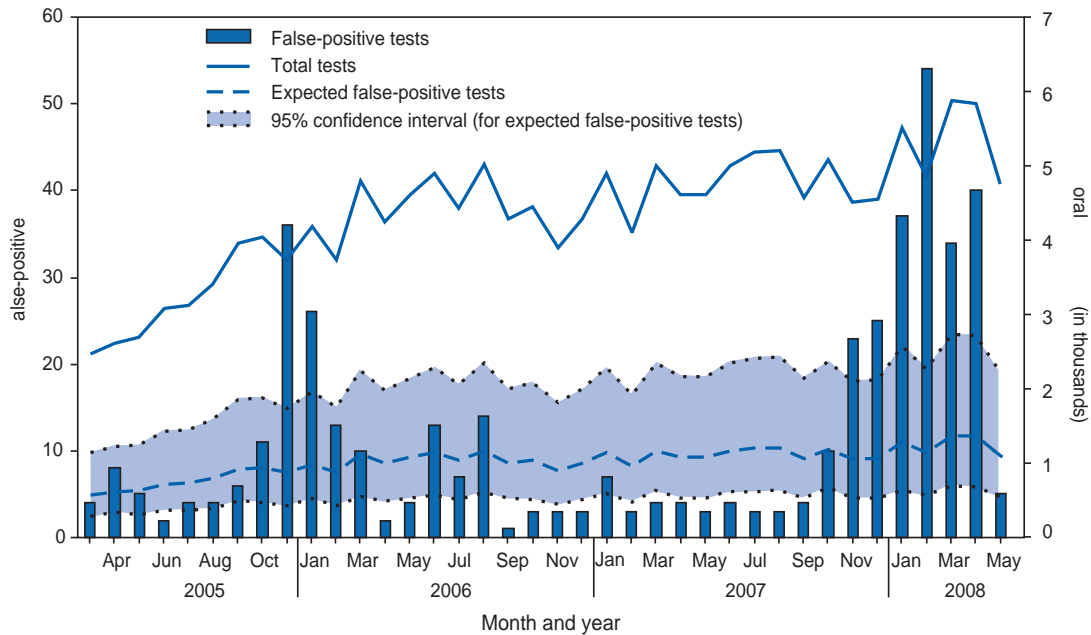
\*The OraQuick rapid HIV test can be used to test either blood (finger-stick or venipuncture whole-blood or plasma specimens) or oral fluid.

The NYC DOHMH Bureau of STD Control routinely offers STD and HIV screening to all patients during the approximately 115,000 annual visits to the 10 STD clinics operated by the city. In 2003, 33,375 conventional (i.e., not rapid) HIV tests were performed. A total of 552 (1.6%) were positive; 79% of all patients tested received their test results. In 2004, after on-site finger-stick whole-blood rapid HIV testing was initiated with the OraQuick test, HIV testing at the clinics increased 14% to 38,092 tests, and receipt of results increased to 88% for HIV-positive and 86% for HIV-negative patients. On average, during January 2004–February 2005, fewer than one false-positive finger-stick whole-blood rapid test occurred monthly. After oral fluid rapid HIV testing began in March 2005, overall test volume increased an additional 24%, to 47,204 tests in 2005. This upward trend in testing has continued (Figure 1); in 2007, the STD clinics performed 60,281 HIV tests, of which 607 (1.0%) were confirmed positive.

In the first 7 months after oral fluid testing was introduced, 35 (0.16%) of 21,722 tests were false positive by Western blot, consistent with the 99.8% (95% confidence interval [CI] = 99.6%–99.9%) specificity claim by the manufacturer in the product package insert (*1*). However, in October 2005, staff members at the clinics noticed an increase in the number of false-positive oral fluid test results each month. From an average of five false-positive tests per month, the monthly number of false-positive tests increased to 11 (0.27% of 4,024 tests) in October 2005 and to 36 (0.97% of 3,735 tests) in November 2005 (with a specificity of 99.03%, lower than the lower limit of the manufacturer's CI specifications) (Figure 1). An investigation detected no consistent relation between false-positive results and test-kit handling, storage conditions, or lot numbers or between false-positive results and clinic sites, test operators, or patient characteristics.

Despite the increased number of false-positive results, testing with the noninvasive oral fluid specimens was popular with clinic patients and more convenient for staff members; therefore, the NYC DOHMH continued offering oral fluid rapid HIV testing while attempting to minimize the adverse

**FIGURE 1. Total number of oral fluid rapid human immunodeficiency virus (HIV) tests administered and number of actual and expected false-positive results,\* by month and year — New York City,† March 2005–May 2008§**



\* As confirmed by Western blot performed on serum. Expected number of false-positive tests and corresponding 95% confidence intervals calculated based on number of oral fluid tests performed monthly and manufacturer's claim for specificity with oral fluid (Orasure Technologies, Inc., OraQuick® Advance Rapid HIV-1/2 Antibody Test customer letter and package insert. Available at <http://www.orasure.com/uploaded/398.pdf>).

† Among patients tested in 10 sexually transmitted disease clinics.

§ Oral fluid rapid HIV tests were introduced in March 2005. They were suspended for 3 weeks in December 2005 and replaced by finger-stick whole-blood testing.

effects of false-positive test results. In late December 2005, a revised strategy was implemented at the clinics by continuing to offer oral fluid rapid tests but immediately following reactive oral fluid tests with a second OraQuick test on finger-stick whole-blood specimens. Both test results were documented in the medical record. Counselors continued to explain to patients that any reactive rapid tests required Western blot confirmation but also emphasized that discordant oral fluid and whole-blood test results were likely to be false positive. By February 2006, an oral fluid test specificity of 99.65% was observed, within the CI of the manufacturer's specifications.

Another persistent increase in false-positive oral fluid test results began in late 2007. Beginning in November 2007, the number of false-positive oral fluid tests increased from 23 (0.51% of 4,503 tests) to a peak of 54 (1.11% of 4,858 tests) in February 2008 (Figure 1). During November 2007–April 2008, the monthly specificity of the oral fluid test ranged from 98.88%–99.49%. In May 2008, fewer false-positive tests occurred; in that month, five (0.11% of 4,749 oral fluid tests) were found to be false positive (specificity: 99.89%).

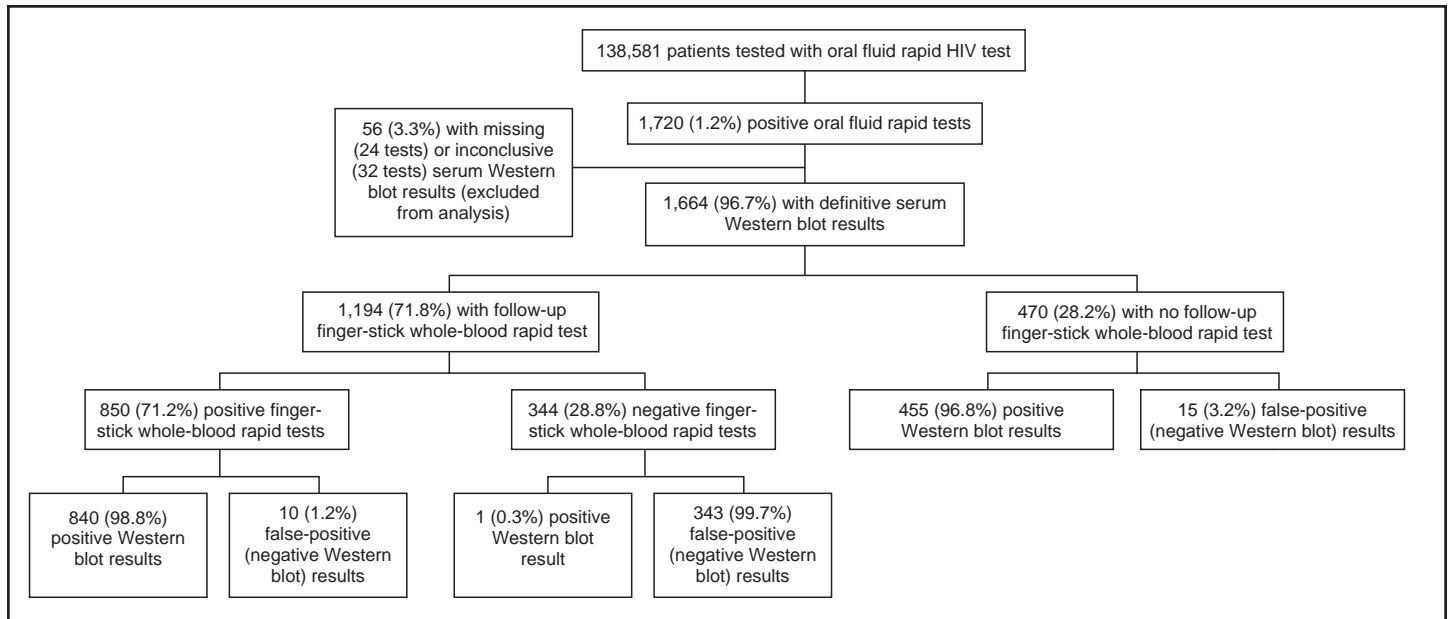
During this second instance of increasing numbers of false-positive oral fluid tests, the clinics continued offering immediate follow-up finger-stick whole-blood rapid tests for all patients with reactive oral fluid tests. The usefulness of the

NYC DOHMH policy was affirmed by the strong correlation between results from whole-blood rapid tests and confirmatory Western blot tests. During December 2005–May 2008, 1,720 patients had reactive oral fluid rapid tests, and definitive Western blot results were recorded for 1,664 (Figure 2). Missing Western blot results (24 patients) and inconclusive Western blot results (32 patients) were excluded from additional analysis. Of these 1,664 patients, 1,194 also provided a finger-stick specimen; 850 (71.2%) had a reactive finger-stick test, of whom 840 (98.8%) were positive by Western blot. Only one (0.3%) of 344 patients with a reactive oral fluid and negative finger-stick whole-blood rapid test was positive by Western blot.

Despite the NYC DOHMH policy that STD clinics should retest using whole-blood specimens after reactive oral fluid tests, 550 patients with reactive oral fluid results did not receive a finger-stick test.† For 80 of these patients, the test

† Before patients were examined by a clinician, STD clinic staff members drew two vials of blood from all patients who visited the clinics (one for syphilis testing and one for confirmation of HIV, if needed). Clinic providers offered the HIV test to all patients; if accepted, providers requested the signed consent form required by the state of New York, and, when the oral fluid test was being used, they conducted the oral fluid rapid HIV test. Patients with reactive oral fluid tests were offered the finger-stick whole-blood test. The clinics were able to obtain confirmation of results for patients who refused the finger-stick test because the initially drawn tube of blood was sent routinely for Western blot confirmation of all reactive tests.

**FIGURE 2. Number and percentage of positive and false-positive oral fluid and finger-stick whole-blood rapid human immunodeficiency virus (HIV) tests, as confirmed by serum Western blot results — New York City,\* December 2005–May 2008**



\* Among patients tested in 10 sexually transmitted disease clinics.

was ordered but not completed; of these, 77 (96.3%) had a positive serum Western blot result. A total of 470 (28.2%) patients with reactive oral fluid tests declined the finger-stick test. Of these, 455 (96.8%) were confirmed positive by serum Western blot, compared with 850 (71.2%) of the 1,194 patients who agreed to a finger-stick test. Additional investigation indicated that 29% of patients with a reactive oral fluid test result who then declined the finger-stick test had been reported previously as HIV-positive to the local HIV/AIDS Reporting System, compared with 21% of patients who agreed to a follow-up finger-stick test.

Although 442 (0.27%) of all 166,058 oral fluid rapid HIV tests performed during March 2005–May 2008 were false positive and demand for rapid HIV testing in NYC DOHMH STD clinics remains high, test operators and counselors have expressed a lack of confidence in oral fluid rapid HIV testing since the abrupt and sustained increase in false-positive test results during November 2007–April 2008. During this period, nearly half of reactive oral fluid tests in the STD clinics were false positive. Of 31,122 patients tested during those 6 months, 213 (0.69%) reactive oral fluid tests were false positive (specificity: 99.31%, below the lower limit of the CI of the manufacturer's specifications) compared with 231 (0.70%) reactive oral fluid tests confirmed positive by Western blot. Consequently, in late May, because results from rapid tests performed on whole-blood specimens were consistently more accurate than those from oral fluid tests and because rapid

testing of whole-blood specimens required fewer additional tests for confirmation of HIV infection, NYC DOHMH again discontinued use of oral fluid specimen testing in STD clinics. Finger-stick whole-blood specimen testing was reinstated as the initial rapid HIV testing method. Oral fluid HIV testing data for May 2008, which became available only after discontinuation of oral fluid testing in the STD clinics, indicated that the recent increase in false-positive oral fluid tests did not continue in May and the test's specificity with oral fluid specimens (99.89%) was within the CI of the manufacturer's specifications; however, rapid HIV testing of oral fluid specimens has not resumed.

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**Editorial Note:** Both the number of patients tested for HIV and the percentage who receive their test results have increased since rapid HIV testing was introduced in the New York City STD clinics in 2004. Nationally, public health laboratories report that rapid tests overall and oral fluid tests specifically account for an increasing proportion of all HIV tests (2), and patients are substantially more likely to receive rapid test results than conventional test results (3). The New York City data in this report underscore the importance of routinely comparing reactive rapid test results with confirmatory

Western blot test results as an essential component of quality assurance in HIV testing (4). Several other jurisdictions have noted clusters of false-positive oral fluid rapid HIV tests since an initial report from Minnesota in 2004 (5–8). Although the causes of these clusters of false-positive tests remain unexplained (6), investigations are under way to determine which specific factors (e.g., test device, site, operator, or oral fluid characteristics of specific patients) might be associated with increased numbers of false-positive test results. Several programs have adopted strategies similar to the one used in New York City and are immediately repeating the rapid test on whole-blood specimens from patients who have reactive oral fluid tests. Other strategies under investigation include repeat testing with a second rapid test from a different manufacturer (9).

The specificity of OraQuick rapid tests performed on oral fluid specimens is lower than that of OraQuick rapid tests performed on whole-blood specimens (5). The test manufacturer's 99.8% specificity estimate with oral fluid is based on a clinical trial of 3,682 participants. In New York City STD clinics, performing approximately 5,000 oral fluid tests per month for 3 years, overall specificity has been 99.73%, but the month-to-month specificity has ranged from 98.88% to 99.98%. Although specificity was lower than the manufacturer's claim during certain months, the test's performance in the New York City clinics was not below the Food and Drug Administration (FDA) minimum threshold of 98% for rapid HIV tests.<sup>§</sup>

Because the prevalence of positive HIV tests has decreased among STD clinic patients concomitant with the increasing number of tests, a slight increase in the percentage of reactive rapid tests that are determined to be false positive (decreased positive predictive value) was expected. However, this change does not account for recurrent clusters of false-positive tests.

The advantages of rapid HIV tests, particularly with oral fluid specimens, include increased availability and acceptability of testing among populations at high risk for HIV infection and increased receipt of test results among those tested (3). The strategy used in New York City, with immediate follow-up using a retest on whole-blood specimens, allowed the STD clinics to continue oral fluid rapid testing while mitigating, somewhat, the adverse effects of false-positive results on both patients and clinic personnel. The strategy also allowed health department staff members to detect the increase in false-positive tests promptly, avert the majority of instances

in which patients might have left the clinic with an oral fluid test result only (e.g., with a false-positive result), and avoid the logistical difficulties inherent with training and maintaining inventory, proficiency, quality assurance, and external controls for rapid HIV tests from more than one manufacturer.

CDC continues to encourage the use of rapid HIV tests because they increase the number of persons who are tested and who receive their test results. Six rapid HIV tests have been approved by FDA since 2002 (10). The New York City data indicate that repeating a rapid test on finger-stick whole blood after receiving a reactive oral fluid test result allows clinic counselors to provide more accurate test-result information to patients while minimizing the number of finger-stick tests that must be performed. Regardless, confirmatory testing is required to confirm both oral fluid and whole-blood reactive rapid HIV tests. Before testing, all patients should be informed that reactive rapid HIV test results are preliminary and require confirmation. In general, testing with blood or serum specimens is more accurate than testing with oral fluid and is preferred when feasible, especially in settings where blood specimens already are obtained routinely.

Overall, oral fluid rapid tests have performed well and make HIV testing possible in many venues where performing phlebotomy or finger sticks is impractical for screening. However, users should be aware of the unexplained variability in the rate of false-positive test results. CDC will continue to work with FDA and the manufacturer to investigate the causes and extent of increases in false-positive oral fluid tests, monitor the performance of oral fluid and other rapid tests to ensure that they continue to perform as expected in testing programs, and investigate other combination test strategies to minimize false-positive test results.

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