

Letters to the Editor

Accuracy of a Saliva Test for HIV Antibody

To the Editor: I question the appropriateness of the recommendation made by King et al. that a single saliva test for human immunodeficiency virus (HIV) antibodies is not sufficiently accurate for screening purposes (1). The authors were too severe in their judgement, neither taking into account public health and personal reasons for screening nor addressing how the accuracy of their saliva assay compares with conventional blood-based enzyme immunoassays (EIA). The main reason for employing screening tests is to concentrate the prevalence of disease in an examined population, making it easier for diagnostic tests to confirm those who truly have the condition. Most screening tests do not correctly identify every person with the disease (i.e., perfect sensitivity) or correctly exclude all those without the disease (i.e., perfect specificity). Instead common screening tests such as Papanicolaou smears, breast self-examination, rectal prostate examinations, or blood cholesterol measurements identify those at higher risk of the disease. When learning of their increased risk, individuals are encouraged to visit their physicians for a more definitive set of diagnostic tests, often done during multiple visits. Many such screening tests are done at home (i.e., blood cholesterol, blood glucose, blood pressure), whereas others requiring professional services are done by trained personnel in a clinic setting. These same notions apply to screening tests for HIV, especially those that use saliva rather than blood to identify the presence of HIV antibodies.

Is the saliva test reported by King et al. that much different from blood assays? In a recent review of 13 current blood assays for HIV antibodies, McAlpine et al. reported a range in sensitivity from 96.9 to 100% and in specificity from 89.9 to 100% (2). All of the blood assays are commercially available and routinely used by clinicians for screening and confirmatory testing. Van Kerckhoven et al. reported similar findings for 36 commercial assays, with a range in sensitivity of 96.6 to 100% and a range in specificity of 85.6 to 100% (3). Sylvester et al. reported higher values in a nonblinded study of four commonly used blood EIAs, ranging in sensitivity from 99.5 to 99.9% and specificity from 99.5 to 99.9% (4). Finally, Malone et al. found for six rapid serological tests that the sensitivity ranged from 89.2 to 100% and the specificity showed values from 56.5 to 100% (5). In a typical diagnostic sequence, such blood-based tests are used first to screen patients to identify and exclude HIV negatives and then to send on for confirmatory testing those who screen HIV positive. If the sensitivity is <100% (as likely occurs in field settings with most commercial EIAs), some persons will be falsely told they are not infected. If the specificity is <100%, other people will be given the false impression that they are HIV infected, until a confirmatory test reveals they do not harbor the virus.

In the results presented by King et al. the saliva assay had a remarkable specificity of 100%. The specimens were gathered with the Omni-Sal collection device (Saliva Diagnostic Systems, Inc.) and analyzed with a single Recombigen HIV-1 EIA (Cambridge Biotech). Thus their saliva test did not falsely report that any person was HIV infected, different from many commercial blood EIAs. The saliva test, however, did miss 2.3% of those who were HIV infected (i.e., sensitivity of 97.7%), as might occur with any screening test or with blood-based assays used in clinical settings. If the saliva specimen had been collected at home, the test described by King et al. would have warned 97.7% of HIV-infected persons that they need to come to a clinic for confirmatory testing, and would have signaled 100% of HIV-negative persons to remain home and not needlessly burden the overextended health care system with additional testing. Given such characteristics and the noninvasive nature of the collection process, the saliva assay of King et al. seems to be an excellent screening tool and is far better for such purposes than other indicators now being used to screen populations for increased risk, such as sexual behavior with multiple partners, drug-injection practices, genital ulcer disease, or circumcision status.

Other than their curious recommendation to not use saliva for HIV screening, I found disquieting the lack of recognition by King et al. of the excellent sensitivity of the GACELISA (Murex Diagnostics, Ltd.), an antibody-capture enzyme immunoassay (EIA) designed especially for low-concentration fluids such as saliva and urine (6). As was summarized elsewhere (7), in 11 published studies dating back to 1987, only one confirmed false negative was reported in saliva tested with the GACELISA. Although we observed six false-negative specimens with the GACELISA in Thailand in the largest comparative investigation of saliva and serum to date, five were field errors in measuring saliva, and one was a labeling error (7). Thus our sensitivity with the GACELISA was 100%, identical to the findings of nine other studies. Since our review, Vall Mayans et al. also reported 100% sensitivity with the saliva-based GACELISA (8).

In their discussion, King et al. implied that the Recombigen HIV-1 EIA with saliva is comparable in sensitivity to the highly regarded GACELISA. Yet their conclusion was based on the sensitivity estimate for a single Recombigen HIV-1 EIA (termed "saliva test protocol I") as compared to our blinded results with the GACELISA in Thailand that was based on at least two of three reactive assays. More properly, they should have compared to our GACELISA findings their Protocol II that featured two EIAs in series. Here the sensitivity was 96.7%, still adequate for screening or surveillance, but lower than the near 100% reported for the GACELISA. In general, their results with the Recombigen HIV-1 EIA are similar to but slightly lower than to our recent saliva findings with the Detect HIV 1/2 assay (BioChemical ImmunoSystems,

Inc.) of 97.7% sensitivity and 100% specificity among 172 true HIV-positive and 814 true HIV-negative persons (9). This is the same assay used by King et al. initially to screen for HIV antibodies in their serum specimens.

Finally, King et al. also made a questionable methodological decision that limits our ability to assess whether their findings are due to the characteristics of their assay or the quality of their laboratory. Investigators have shown that laboratory errors are common, whether measuring HIV antibodies in saliva (7) or in blood (10–12). For this reason, it is important to present the findings as reported direct from the field (i.e., done in a blind manner with both assay and field errors) and then reanalyze the discrepant specimens to estimate the extent of field errors. This was not done by King et al. Instead, the authors attempted to make a virtue of their omission by writing, “reexamination of only the discordant cases has a high likelihood of introducing an optimistic bias into estimates of test performance (since concordant samples are not subject to similar scrutiny), and in our opinion the results of such reexamination should not supersede the initial blinded assessment of specimens.” Although I understand their concern, it is disconcerting that they have not offered readers the choice of viewing both an initial blind analysis and a follow-up analysis of discrepant pairs. With this omission, King et al. leave us to ponder if miscoding, mislabeling, and similar problems account for their findings, or are the false-negative results due only to the limits of the Recombigen HIV-1 EIA with saliva.

Ultimately we need to keep in mind that the objective of HIV screening is to increase awareness of viral infection in the population (13). At this time, our only means to this end is with HIV antibody testing. For various reasons, many people at risk of HIV are not being tested. As concerned health professionals, we need to reach these people, likely with home HIV tests (14). Our intent should be to encourage personal screening so that those likely to be HIV infected will visit their doctor for confirmatory (or diagnostic) testing and will learn through proper counseling how to avoid further transmission of the virus (15). To this end, saliva appears to be an excellent medium for popularizing eventual widespread screening.

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REFERENCES

1. King A, Marion SA, Cook D, et al. Accuracy of a saliva test for HIV antibody. *J Acquir Immune Defic Syndr Hum Virol* 1995;9:172–5.
2. McAlpine L, Gandhi J, Parry JV, et al. Thirteen current anti-HIV-1/HIV-2 enzyme immunoassays: how accurate are they? *J Med Virol* 1994;42:115–18.
3. Van Kerckhoven I, Vercauteren G, Piot P, et al. Comparative evaluation of 36 commercial assays for detecting antibodies to HIV. *Bull World Health Organ* 1991;69(6):753–60.
4. Silvester C, Healey DS, Cunningham P, Dax EM. Multisite evaluation of four anti-HIV-1/HIV-2 enzyme immunoas-

5. Australian HIV Test Evaluation Group. *J Acquir Immune Defic Syndr Human Retrovirol* 1995;8:411–19.
6. Malone JD, Smith ES, Sheffield J, et al. Comparative evaluation of six rapid serological tests for HIV-1 antibody. *J Acquir Immune Defic Syndr* 1993;6(2):115–19.
7. Connell JA, Parry JV, Mortimer PP, et al. Novel assay for the detection of immunoglobulin G anti-human immunodeficiency virus in untreated saliva and urine. *J Med Virol* 1993;41:159–64.
8. Frerichs RR, Silarug N, Eskes N, et al. Saliva-based HIV antibody testing in Thailand. *AIDS* 1994;8:885–94.
9. Vall Mayans M, Casabona J, Rabella N, et al. Comparison of saliva and serum for HIV testing among populations with high risk behaviors. *Eur J Clin Microbiol Infect Dis* 1995 (in press).
10. Wongba C, Pagcharoenpol P, Eskes N, et al. HIV saliva test for surveillance and surveys. *AIDS* 1995 (in press).
11. Gerber AR, Valdiserri RO, Johnson CA, et al. Quality of laboratory performance in testing for human immunodeficiency virus type 1 antibody. Variables associated in multivariate analyses. *Arch Pathol Lab Med* 1991;115:1091–6.
12. Snell JJ, Supran EM, Tamashiro H. WHO international quality assessment scheme for HIV antibody testing: results from the second distribution of sera. *Bull World Health Organ* 1992;70(5):605–13.
13. Snell JJ, Supran EM, Esparza J, et al. World Health Organization quality assessment programme on HIV testing. *AIDS* 1990;4(8):803–6.
14. Frerichs RR. Personal screening for HIV in developing countries. *Lancet* 1994;343:960–2.
15. Bayer R, Stryker J, Smith MD. Testing for HIV infection at home. *N Engl J Med* 1995;332:1296–9.
16. Frerichs RR. HIV winners and losers. *Epidemiology* 1995;6(3):329–31.

Recent Trends in *Pneumocystis carinii* Pneumonia as AIDS-Defining Disease in Nine European Countries

To the Editors: Dr. Delmas and colleagues (1) recently investigated the trends of *Pneumocystis carinii* pneumonia (PCP) as an AIDS-defining disease in Europe. Although perhaps not exact, there did appear to be a sizeable colder climate to warmer climate trend in occurrence of *P. carinii* pneumonia as an initial AIDS illness in their data. Countries with Mediterranean climates, such as Portugal and Italy, had lower levels of PCP AIDS, ~28%, than did those with colder climates, such as Germany and the United Kingdom, 38.4 to 48.2%. Although this is not totally clear from the analysis presented in the article, the trend appeared to remain after adjustment for risk group, age group, and year of diagnosis. The authors suggested that perhaps pathogens responsible for other AIDS diseases (such as tuberculosis and toxoplasmosis) occurred more frequently in Southern European countries, and consequently PCP was seen less as an AIDS-defining illness in these areas. However, they did not directly speculate on the possibility of geographical differences in rates of infection with *P. carinii* or in progression of a subclinical *P. carinii* infection to disease.

In 1991, we noted (2) a similar (albeit small, but statistically significant) trend among AIDS cases in the American Multicenter AIDS Cohort Study (MACS) (3) of homosexual men. Cities with colder climates (Pittsburgh