Alternative Test Sequences for HIV Screening of Donated Blood

Harriet H. Imrey, Ph.D., and Ben T. Williams, M.D.

Human Immunodeficiency Virus (HIV) infection is extremely rare among volunteer blood donors. The highly sensitive Enzyme Linked Immunoassay (ELISA) test and the highly specific Western blot confirmation constitute the test sequence now used to minimize the possibility of transfusion associated HIV infection and to minimize the loss of donors due to false positive test results. The estimated operating characteristics for the test sequence permit the estimation of true infection rates which may be higher or lower than "observed" rates among subcategories of blood donors with progressively lower prevalence rates. The probability that a positive test result indicates true infection also declines with decreasing prevalence. The potential benefits of changing the test sequence so that complete HIV screening is implemented only for donations which are hepatitis-free include a reduction in the costs of Western blot testing and donor counseling, a reduction in the number of donors who use the blood bank inappropriately for personal HIV testing, and a more explicit recognition of the false positive problem when counseling donors.

INTRODUCTION

A screening test, in contrast to a diagnostic test, is usually intended to give information about higher or lower risk for a disease outcome instead of a diagnosis. The predictive value of a positive screening test is usually low, on the order of 25% to 50%, but the personal and financial costs of follow-up with more specific diagnostic tests are frequently outweighed by the fact that a significant portion of potential cases of the disease are included within the relatively small group of positive screenees. A screening test is generally considered to be in the best interests of the screening population if (1) the test identifies a higher risk for a serious disease which can be cured or ameliorated if detected early, and (2) the test has sensitivity and specificity characteristics which are moderately high relative to the prevalence of the disease—the prior probability—in the screened population.

Screening of voluntary blood donors for the Human Immunodeficiency Virus (HIV) is based on very different considerations. Safety of the blood supply depends upon
screening techniques which are maximally sensitive (i.e., the procedure should involve identifying the largest possible fraction of potentially contaminated blood); specificity is a secondary, although important, consideration. For instance, a hypothetical screening test which was 0.9999 sensitive, but only 0.5 specific, would not be a practical option, because disposing of 50% of all blood donations would be contrary to the best interests of the donor, the patient and the public.

Evaluation of the results of a screening test is dependent upon the prevalence of the condition in the population. This rule is repeated frequently during the medical education process and in the professional literature. There are a number of epidemiologic procedures which are appropriate only when a disease is "rare," meaning a prevalence of $\pm 0.01^1$. Most successful screening efforts, such as those for breast, cervical or colorectal cancers are predicated upon a "very rare" population prevalence (i.e., $p = \pm 0.001$). When the condition being screened for is very, very rare ($p \leq \pm 0.0001$) the cost:benefit ratio changes in a nonlinear and nonintuitive fashion.

The combination of the enzyme-linked immunoassay (ELISA, or EIA) and Western blot (WB) tests has been demonstrably effective as a screening method for removing potentially HIV-contaminated units from the national blood supply. If considered as a diagnostic test (to inform donors of their HIV status) rather than as a screening test (to remove suspect donations from the blood supply), it is much less adequate. The reason is that HIV infection is a very, very rare condition among the blood donor population; a blood donor who is considered a confirmed HIV carrier may be falsely positive.

### ACCURACY OF HIV SCREENING TESTS

When blood screening was first implemented in 1985, operating characteristics of tests and test sequences were estimated by the Centers for Disease Control.\(^2\) The ELISA test was estimated to have a sensitivity of 0.985 and a specificity of 0.998; the Western Blot test parameters, contingent upon a repeatedly reactive ELISA test, were estimated to be sensitivity = 0.92 and specificity = 0.95. The joint specificity of the test sequence at the time was $1 - (1 - 0.998)(1 - 0.95) = 0.9999$.

In 1987 the College of American Pathologists, in conjunction with the American Association of Blood Banks, conducted an open proficiency testing program for laboratories which conducted HIV antibody tests.\(^3\) The laboratories which volunteered to participate in the proficiency test program reported mean ELISA test parameters of sensitivity = 0.995 and specificity = 0.983. Values for the Western Blot test averaged sensitivity = 0.892 and specificity = 0.948. These averages include results obtained from reference laboratories, to which average proficiency was compared (see Table 1).

A misclassification (i.e., a false positive or a false negative) in a screening test may be a function of the technique, the technician, the specimen, clerical error, or of interactions among them. The ELISA technique—the licensed test procedure, including reagents and automated equipment—is extremely sensitive and specific. The reference laboratories which participated in the CAP proficiency test achieved 100% sensitivity when testing samples known to be antibody-positive, clearly the best sensitivity inherent in the technique, without any technician error. The 99.8% sensitivity reported by other laboratories may reflect a minimum misclassification rate attributable to technician error.