

HIV SCREENING WORKSHOP

Exercise

INTRODUCTION:

Since its first discovery in 1981, AIDS became a pandemic. Worldwide, actually over 30 million people are living with HIV (i.e., are infected by the human immunodeficiency virus), or with AIDS (i.e., are suffering from the acquired immune deficiency syndrome), respectively, with yearly about 5 million people dying from AIDS, and with yearly about 5 million new HIV-infections. In Germany, today there are about 37.000 HIV infected people, 5000 of whom living with AIDS and about 500 yearly dying from it, and, last but not least 2000 new HIV-infections.

The infection with the HI-virus leads to AIDS after on average 10 years of incubation time. Slowly, but continuously, an important part of the immune-system, mainly affecting the T-Helper-Cells, is worsening. People then, together with a dramatic reduction of their general condition, suffer from „opportunistic infections“ (i.e. AIDS) and die.

Since 1984, HIV is known as the cause of the disease. Since 1985, there are different HIV blood-tests available, actually usually performed as two antibody tests (ELISA/EIA and Western Blot, see below) and an antigen test (PCR, so called „viral load“). Since 1996, there is an effective drug treatment available (but at high costs regarding drug side effects and an uncertain perspective due to emerging virus resistance). A vaccination is not yet available.

GOAL:

The goal of this workshop is to focus on the problems associated with screening various groups of individuals for HIV (with an antibody test) to develop an understanding of the principles of screening in populations with differing prevalences of the condition to be detected, and to apply that knowledge to clinical practice.

SPECIFIC OBJECTIVES:

After completing this workshop the student should be able to:

1. Define, derive, and interpret measures of sensitivity, specificity, positive and negative predictive value.
2. Discuss the trade-offs between sensitivity and specificity.
3. Describe the relationship between prevalence and predictive value (positive and negative PV).
4. Apply such measures to clinical decision-making.
5. List the principles of a good screening program.

STUDENT ASSIGNMENTS:

Discuss the clinical scenario, develop a learning agenda, work through the exercise and draw conclusions which help you understand the screening issues and apply that understanding to clinical decision-making.

CLINICAL SCENARIO:

Review the following clinical scenario and think about how to approach the problem presented, also feel free to discuss this with classmates.

One of your patients, a 28 year old married woman, has consulted you. She reports that she followed a televised call for blood donors from the Red Cross. When she completed their background risk factor questionnaire, she was advised *not to donate* because a history of blood transfusion put her at risk of HIV positivity. (She sustained a lacerated liver in an automobile accident in 1995 in Poland and was transfused 3 units of whole blood). She reports that she has never been „tested for AIDS“. She now is quite scared - she doesn't know:

- what to tell her husband
- if she and her husband should be tested for HIV, or even,
- „if they should use condoms during sexual activity“.

How would you handle this situation?

For help in interpreting the significance of a positive (or a negative) HIV-test, you decide to consult an older colleague (Dr R.B.) who is involved in the HIV/AIDS field for some years.

Dr. R.B. describes the situation.

SCREENING FOR ANTIBODY TO THE HUMAN IMMUNODEFICIENCY VIRUS

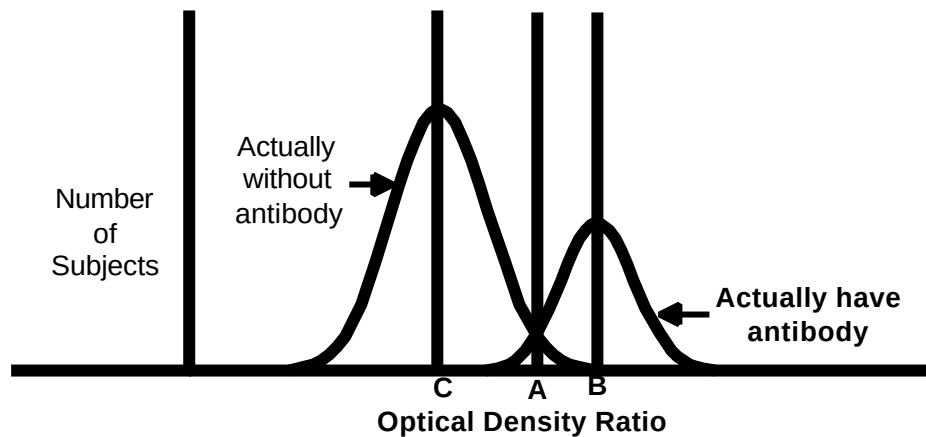
PART I

The first AIDS cases in 1981/82 mainly came from the so called „risk groups“ of homo-/bisexual men and injecting drug users (IDU, also known as „IVDU“, for intravenous drug users, or „IVDA“, for abusers, respectively). Firstly in December 1982, a report in the *MMWR* described also three persons who had developed AIDS but who had neither of the risk factors mentioned above. These three persons had previously received whole-blood transfusions. By 1983, widespread recognition of the problem of transfusion-related AIDS led to recommendations that persons in known risk groups voluntarily should be prevented from donating blood. In June 1984, after the discovery of HIV, the first companies were licensed to produce enzyme-linked immunosorbent assay (ELISA or EIA) test kits for detecting HIV antibodies in the blood. Finally, the new test became available from March 1985, the date the first test was approved by the FDA (Federal Drug Administration, USA).

EIA results are recorded as „optical-density“- (OD-) ratios. The OD ratio is the ratio of absorbance of the tested sample to the absorbance of a control sample. The greater the OD ratio, the more „positive“ the test result is. The EIA, as with most other screening tests for various diseases, is not „perfect“; there is some overlap of optical-density ratios of samples that are actually antibody positive and those that are actually antibody negative. This is illustrated in the following figure.

Establishing a „cutoff“ value to define a positive test result from a negative one is somewhat arbitrary. You initially decide that optical density ratios that are greater than „A“ on the above figure are positive. This is illustrated in the following figure.

**Hypothetical distribution of results of an EIA for HIV,
by actual antibody status**



Definitions:

Sensitivity is the ability of a test to detect a disease when it is present.

Specificity is the ability of a test to indicate nondisease when no disease is present.

QUESTION 1a: In terms of sensitivity and specificity, what happens if you raise the cutoff from "A" to "B"?

QUESTION 1b: In terms of sensitivity and specificity, what happens if you lower the cutoff from "A" to "C"?

QUESTION 2: From what you know now, what is the relationship between sensitivity and specificity of a screening test.

1985, when the first HIV antibody test kits arrived in blood banks worldwide, the sensitivity of these „early“ test kits was 95.0% (0.95) and the specificity was 98.0% (0.98).

Today, these tests have much improved, but for better demonstration of the screening issues we will calculate with these old parameters.

QUESTION 3: With this information, construct a 2-by-2 table, calculate the positive predictive value (PPV) and negative predictive value (NPV) of the EIA in a hypothetical population of 1,000,000 blood donors. Assume that the actual prevalence of HIV antibody among blood donors is 0.04% (0.0004). Using a separate 2-by-2 table, calculate PPV and NPV for a population of 1,000 IDU; assume the prevalence of HIV antibody among drug users is 10.0% (0.10).

(Note: these prevalence data are factitious ! In Germany, for blood donors the actual value is about 1 per 100.000 (0,001 % or 0,00001), whereas in IDU the prevalence is much dependent on place of living or belonging to different subgroups, but might be estimated *on average* with 10 %)

Blood Bank Calculations:

Test Result	Standard			Predictive Value	
	Present	Absent	Total		
Present				Pos->	
Absent				Neg->	
Total				<--Prevalence	
Sensitivity->			<-Specificity		

Drug Clinic Calculations:

Test Result	Standard			Predictive Value	
	Present	Absent	Total		
Present				Pos->	
Absent				Neg->	
Total				<--Prevalence	
Sensitivity->			<-Specificity		

This EIA was proposed as a test for *blood donor screening*. However, there was concern about the possibility that some antibody-positive units would be missed by the test. Also, there would have to be a notification procedure for EIA-positive donors if the test was used, so false-positive tests were a concern.

QUESTION 4: Do you think that the EIA is a good screening test for the blood bank? What would you recommend to the blood bank directors about notification of EIA-positive blood donors?

The National Drug Council of Germany noticed that the HIV-prevalence among IDU is somewhat about 10%. He wants to do a voluntary HIV antibody seroprevalence survey of clients in a drug treatment clinic for planning purposes and would like to assess the feasibility of using the test results as part of behavior-modification counseling.

QUESTION 5: Do you think that the EIA performs well enough to justify informing test-positive clients in the drug abuse clinics that they are positive for HIV?

QUESTION 6: If sensitivity and specificity remain constant, what is the relationship of prevalence to positive predictive value and negative predictive value?

QUESTION 7: What would the blood bank director and the head of the drug treatment clinic consider in deciding where the OD cutoff point should be for each program? Who would probably want to lower the cutoff value?

PART II

There was a concern that, because of the low positive predictive-value of the EIA in the blood donor population, the blood bank personnel could not properly inform those who were EIA positive of their actual antibody status. For this reason, evaluation of the Western Blot as a confirmatory test for HIV antibody was suggested.

The Western Blot test identifies antibodies to specific proteins associated with HIV. The Western Blot is the most widely used secondary test to detect HIV antibody because its specificity exceeds 99.99%; however, it is not used as a primary screening test because it is technically difficult to perform and expensive. Its sensitivity is thought to be lower than that of the EIA (about 80%).

The blood bank director wondered whether the initial EIA-positive results could either be confirmed by repeating the EIA or by using the Western Blot, considering persons to have the antibody only if results of both tests are positive.

Compare the performance of the repeated EIA and the Western blot as confirmatory tests. To do this, use your earlier hypothetical sample of 1,000,000 blood donors. Assume that serum specimens that are initially positive by EIA are then split into two halves; a repeat EIA is performed on one half and a Western Blot on the other.

QUESTION 8: What is the actual antibody prevalence in the population of persons whose blood samples will receive confirmatory testing?

QUESTION 9: Calculate the predictive-value positive of the two sequences of tests: EIA-EIA and EIA-Western Blot. Assume that the sensitivity and specificity of the EIA are 95.0% and 98.0%, respectively.

EIA-EIA

Test Result	Standard			Predictive Value	
	Present	Absent	Total		
Positive				Pos->	
Negative				Neg->	
Total				<--Prevalence	
Sensitivity->			<-Specificity		

EIA-WB

Test Result	Standard			Predictive Value	
	Present	Absent	Total		
Positive				Pos->	
Negative				Neg->	
Total				<--Prevalence	
Sensitivity->			<-Specificity		

* NPV is derived by combining the negative rows from the two tables EIA-EIA or EIA-WB

QUESTION 10: Why does the predictive-value positive increase so dramatically with the addition of a second test? Why is the predictive value positive higher for the EIA-WB sequence than for the EIA-EIA sequence?

Part III

In 1987 the Governor of the State of Illinois / USA asked the State Epidemiologist to evaluate a proposed premarital HIV-antibody-screening program. A bill to establish the program was scheduled to be introduced into the legislature. It was estimated that 60,000 persons per year married in the State. The proposed legislation required that each prospective bride and groom submit a blood sample for EIA testing. Those with a positive EIA test would have a Western blot done.

The goal of the screening program was to decrease inadvertent mother-child or sexual HIV transmission by determining who among those to be married are probably infected with the virus.

QUESTION 11: What criteria would you consider in evaluating this screening program?

1. The condition being sought should be an important health problem, for the individual and/or the community.
2. The natural history of the condition, including its development from latent to declared disease, should be adequately understood.
3. There should be a recognizable latent or early symptomatic stage.
4. There should be a suitable screening test or examination for detecting the disease at the latent or early symptomatic stage, and this test should be acceptable to the population.
5. There should be an acceptable form of treatment for persons with recognizable disease or intervention to lower risk of disease in the population.
6. Treatment at the presymptomatic, early stage of a disease should favorably influence its course and prognosis in the individual or lower the risk to the population.
7. There should be an agreed policy on whom to treat.
8. The facilities required for diagnosis and treatment of patients revealed by the screening program should be available.
9. The cost of case-finding (which would include the cost of diagnosis and treatment) needs to be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process, not a „once and for all“ project.

QUESTION 12: What should be the final recommendation of the State Epidemiologist to the Governor?

POSTSCRIPT: (back to the clinical scenario at the beginning)

Dr. R.B. asks if you know whether the blood your patient received had been screened for HIV. Her transfusions were in 1995, when screening for HIV was widely available, also in Poland. You find that she was transfused at an academic center that screened properly, and her blood was most probably screened. You learn from the Polish health authorities that the best estimate of the risk of seroconversion for HIV due to blood transfused 1995 that has been screened was 1 in 100,000 or 0.001% (note: this number again is fictitious and especially in East Europe after 1995 strongly dependent on country, place, and time)

QUESTION 13: Based on this information, would you consider your patient to be in a high risk group? She is concerned about what to tell her husband about this episode - how would you advise her?

QUESTION 14: Based on the data above, would you advise her to use condoms during sexual activity if her EIA test was negative? Would you advise her husband to be tested?

Many issues raised about screening for HIV antibody are applicable to diagnostic tests in general. The ideal diagnostic test would always give the right answer - a positive result in everyone with the disease, and a negative result in everyone else - and would be quick, safe, reliable, and inexpensive. Few, if any tests are that ideal.

QUESTION 15: Are there differences in using a diagnostic test in someone who has symptoms and in someone in whom it is being used solely for screening purposes?

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