HYLAND THERAPEUTICS
DIVISION OF TRAVENOL LABORATORIES, INC.

cc - S. Holst
7-11-83 S. Kuwahara

Interoffice correspondence

to: J. Bacich DICK THOMAS

date: June 27, 1983

from: W. Slimak

copies: R. A. DeVreker
J. L. Goodman, M.D.
H. Kingdom, M.D.
M. Lee
H. Termeer
R. L. Thomas

subject: Summary of AIDS Testing [illegible]
Meeting of June 22, 1983

The purpose of this meeting was to bring the Glenoaks group up-to-date on information gathered concerning a testing system (serrogate or real) to screen for AIDS. The information has been obtained from literature research, and discussions with the CDC and colleagues in the industry. Attendees at the meeting were myself, J. Bacich, R. DeVreker, J. Goodman, M. Lee and R. Thomas. The tables of data presented in this report were obtained from the CDC (B. Evatt and R. Ramsey): some of these data have not been made public, therefore, this report must be treated in strict internal confidence. My contacts at the CDC are B. Evatt, S. McDoggle, R. Ramsey and T. Spira. My contact at Ortho is R. Reckle and Roche is J. Bookout. Several topics were discussed and will be presented in this report.

- Current Data

  Tables 1-5 were presented to bring the group up-to-date on current data available from the CDC.

  Table 1 is a presentation of various test systems which have been applied to the detection of AIDS. As a note, Specificity relates to a test system ability to detect "negative": no False negative equals 100% Specificity. Alternately, Sensitivity relates to a test system ability to detect "Positives": no False positive equals 100% Sensitivity. The data in Table 1 is divided in three categories: Low Sensitivity, High Specificity; High Sensitivity, Low Specificity; and High Sensitivity, High Specificity. Two test systems whch have received much recent publicity are Beta$_2$ Microglobulin and thymosin α-1. Both these test systems would be in the first category: Low Sensitivity, High Specificty (too many False positives). A third test system, Human T-cell Leukemia Virus (HTLV), has also been mentioned. At present, the HTLV is a highly technical system involving cell culture, cell harvesting, cell labeling and microscopic differential of cells. It should be noted that most researchers and the CDC feel that the causitive agent for AIDS is a retrovirus, possibly a variant of HTLV. As information is available on HTLV, it will be passed on.

  Table 2 is a presentation, by group, of data obtained using T Helper cell to T Suppressor cell ration (Th/Ts) and Absolute Lyphocyte Count. A weighted average for detection of AIDS (Specificity) is 80.5% for Th/Ts and 74.4% for Absolute Lympocytes. An estimate of the False positive rate (normal population) is 3.1% for Th/Ts and approximately 5% for Absolute Lymphocyte Count.

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- Current Data (continued)

Table 3 is a presentation, by group, of data obtained using Anti-HBc and Anti-HBs. A weighted average for detection of AIDS is 87.5% for Anti-HBc and 75.0% for Anti-HBs. Estimates for both test systems in the normal population is approximately 5%. Published data and experience shows a "False" positive rate in donor population to be between 10% and 12%.

Table 4 is a presentation, by group, of data obtained from two Immune Complex test systems - Staph Binding Assay (SBA) and CIQ Binding Assay (CIQBA). A weighted average for the detection of AIDS is 79.8% for SBA and 58.2% for CIQBA. Estimates of False positive rates are 1.6% for SBA and 2.6% for CIBQA. Recent data have been obtained on a third Immune Complex assay - C3-d presently under research by Ortho. Estimates of Specificity is approximately 86% and Sensitivity is approximately 97%. Unlike the SBA system, which is a semicomplicated (3) day procedure, the C3d system is a 3 hour ELISA methodology system. Initial data look very promising for the C3d system.

It should be pointed out that in reviewing the data in Tables 2-4, no one test system has a Specificity greater than 87.5% for detecting AIDS: that is to say, the best test system (Anti-HBc) misses 12.5% of AIDS. Table 5 is a presentation of parallel screening using two test systems. A person was considered positive if positive by one or both the systems used. Three test system combinations are presented: Absolute Lymphocyte Count/SBA, Absolute Lymphocyte Count/Anti-HBc, and SBA/Anti-HBc.

A review of these data indicate the following:

- Absolute Lymphocyte Count/SBA combination indicates no improvement over Anti-HBc alone, for Specificity.
- Absolute Lymphocyte Count/Anti-HBc indicates improved Specificity over Anti-HBc alone.
- SBA/Anti-HBc indicates excellent Specificity 98.4% for AIDS and very good detection of high risk groups.

Discussion/Recommendations

Of all the data available, Anti-HBc stands out as the best single test system, 87.5% Specificity for AIDS. The disadvantages of this system are:

1) a failure to detect approximately 12.5% of the AIDS
2) an estimated "False" positive rate in our donor system of 10-12%

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Discussion/Recommendations (continued)

This is a costly loss of donors for only a 87.5% detection of AIDS. The most impressive data to date is the parallel test system of SBA/Anti-HBc. This system clearly is able to detect 98.4% of AIDS. Although the estimated False positive rate for this system is approximately 15%, one could say that the system detects virtually all AIDS. To add to this is the fact that the Immune Complex system by Ortho (C3d) is more specific for AIDS than the SBA.

It is my recommendation that the following screening be considered for detection of AIDS in our donor population:

1) Screen all donors once for Anti-HBc. The HB_sAg will be the marker on a continuing basis.
2) Screen each bleed for Immune Complex. At this point, I would recommend the Ortho C3d system. This system is technically simple (ELISA), can be performed in 3 hours, and uses plasma as a specimen.

Cost Analysis

- Anti-HBc

If it is assumed that first two months, 50,000 donor/month will be tested and 10,000 donor/month will be tested after that, a total of 220,000 tests will be performed the first year. Abbott has quoted a price of $2.40/test. It is estimated that 4 technicians will be added to handle testing and sample processing. Cost/technician is $1,500/technician/month or $18,000/technician/year.

Test Kit	220,000	x	$ 2.40	=	$528,000
Technicians	4	x	$18,000.00	=	72,000
Other Supplies			$12,000.00	=	12,000
					$612,000

The cost/liter, based on 1,500,000 liters, is $0.41/liter.

- Immune Complex

It is assumed that the cost of the test is between $0.50 - 1.00/test. It is estimated that approximately 18 technicians will be needed to test and sample process the additional samples.

Estimate High

1,500,000 liters x 1.5 test/liter x $1.00	=	$2,250,000
18 Technicians x $18,000	=	324,000
Other Supplies	=	20,000
		$2,594,000

or $1.73/liter

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Cost Analysis (continued)

Estimate Low

1,500,000 liters x 1.5 test/liter x $0.50	=	$1,125,000
18 Technicians x $18,000	=	324,000
Other Supplies	=	20,000
		$1,469,000

or $0.98/liter

- Total Cost

The cost/liter of the total test system is estimated to be between $1.39/liter to $2.14/liter.

Implementation

In order to implement the recommended test system for AIDS (Immune Complex/Anti-HBc), two major considerations are apparent:

1) The time required to obtain test kits and qualify them, the time required to retain and train technicians, and the time required for programming changes to allow 100% inspection to be utilized.
2) A large enough supply of plasma and donors to accommodate the False positive rate of the test system.

Item 1 will require 8-12 weeks depending on supply of Immune Complex test kits and programming changes. Anti-HBc could be implemented in approximately 4 weeks if used as the sole test.

Item 2 is very complicated. At present, plasma supply is the major issue in Bioprocurement. Until the plasma supply increases substantially, the AIDS screening would not be feasible. A possible alternate supply of plasma could be the prison system. If the testing could insure "clean" plasma for AIDS, I feel the prison plasma is viable.

Please contact me if there are any questions or comments.

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Bill
jom
Attachments

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TABLE-1

SENSITIVITY AND SPECIFICITY OF TESTS FOR IDENTIFYING INDIVIDUALS AT RISK OF TRANSMITTING AIDS

Low Sensitivity, High Specificity

- Immunoglobulin G level
- Immunoglobulin A level
- Immunoglobulin M level
- Hepatitis B surface antigen
- MHA - TP

High Sensitivity, Low Specificity

- EBV VCA, EBNA, EA
- CMV CF, IHA
- HSV CF, 1HA1, 1HA2
- Anti-Hepatitis A antigen

High Sensitivity, High Specificity

- Absolute Lymphocyte Count
- T helper cell to T suppressor cell ratio (Th/Ts)
- Immune Complexes - Staph Binding Assay (SBA)
  - C1q Binding Assay (C1qBA)
- Anti-Hepatitis B Core Antigen (Anti-HB_c)
- Anti-Hepatitis B Surface Antigen (Anti-HB_s)

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TABLE-2

FREQUENCY OF ABNORMAL TESTS BY GROUP - I

	TH/TS %≤1.0 (N)	ABSOLUTE LYMPHOCYTES %≤1500/CMM (N)
AIDS CASES		
HOMOSEXUALS/BISEXUALS	77.4 (53)	69.6 (56)
IV DRUG USERS	100.0 (11)	92.3 (13)
HAITIANS	100.0 (15)	73.3 (15)
OTHERS	37.5 (8)	70.0 (10)
PROBABLE AIDS		
LYMPHADENOPATHY	52.1 (71)	19.1 (68)
RISK GROUP "CONTROLS"		
HOMOSEXUALS/BISEXUALS	19.7 (61)	12.1 (58)
HAITIANS	9.1 (11)	0 (11)
NORMAL CONTROLS	3.1 (33)	~ 5

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TABLE-3

FREQUENCY OF ABNORMAL TESTS BY GROUP - II

	ANTI-HB_C % POSITIVE (N)	ANTI-HB_S % POSITIVE (N)
AIDS CASES		
HOMOSEXUALS/BISEXUALS	88.2 (93)	81.9 (94)
IV DRUG USERS	100.0 (21)	61.9 (21)
HAITIANS	86.7 (15)	66.7 (15)
OTHERS	42.9 (7)	33.3 (6)
PROBABLE AIDS		
LYMPHADENOPATHY	81.3 (64)	75.4 (61)
RISK GROUP "CONTROLS"		
HOMOSEXUALS/BISEXUALS	79.2 (149)	79.5 (146)
HAITIANS	36.2 (116)	39.3 (107)
NORMAL CONTROLS	~5	~5

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TABLE-4

FREQUENCY OF ABNORMAL TESTS BY GROUP - III

	SBA %>31U (N)	C1qBA %≥8% (N)
AIDS CASES		
HOMOSEXUALS/BISEXUALS	77.8 (45)	55.6 (45)
IV DRUG USERS	80.0 (15)	53.3 [redacted]
HAITIANS	100.0 (13)	76.9 [redacted]
OTHERS	50.0 (6)	50.0 (6)
PROBABLE AIDS		
LYMPHADENOPATHY	93.3 (60)	75.4 (61)
RISK GROUP "CONTROLS"		
HOMOSEXUALS/BISEXUALS	62.5 (32)	45.5 (33)
HAITIANS	18.2 (11)	9.1 (11)
NORMAL CONTROLS	1.6 (122)	2.6 (114)

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TABLE-5

FREQUENCY OF ABNORMAL TESTS BY GROUP - PARALLEL SCREENING

	SBA ≥31U
Absolute Lymphocyte County <1500/cmm	
AIDS Cases	88.7 (53)
Lymphadenopathy	100.0 (49)
Homosexual/Bisexual "Controls"	56.0 (25)
Haitian "Controls"	76.5 (17)

	Anti-HB_c Positive
Absolute Lymphocyte Count <1500/cmm	
AIDS Cases	96.1 (77)
Lymphadenopathy	88.6 (44)
Homosexual/Bisexual "Controls"	86.0 (50)
Haitian "Controls"	30.0 (10)

	Anti-HB_c Positive
SBA ≥31U	
AIDS Cases	98.4 (62)
Lymphadenopathy	97.5 (40)
Homosexual/Bisexual "Controls"	92.3 (26)
Haitian "Controls"	50.0 (10)

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