DEPARTMENT OF THE NAVY
BUREAU OF MEDICINE AND SURGERY
2300 E STREET NW
WASHINGTON DC 20372-5300

IN REPLY REFER TO

BUMEDINST 6220.10
BUMED-24
26 Apr 93

BUMED INSTRUCTION 6220.10

From: Chief, Bureau of Medicine and Surgery
To: Ships and Stations Having Medical Department Personnel

Subj: MANAGEMENT OF HUMAN T LYMPHOTROPIC VIRUS TYPE I and II (HTLV I/II) INFECTION IN THE NAVY AND MARINE CORPS

Ref: (a) SECNAVINST 5300.30C

Encl: (1) HTLV I/II Infection: Testing, Notification, and Counseling Policies and Procedures
(2) Guidelines for Repeatedly Reactive HTLV-I Specimens
(3) Licensure of Screening Tests for Antibody to Human T-Lymphotropic Virus Type I, U.S. Public Health Service, Centers for Disease Control, Morbidity and Mortality Weekly Report, 1988, 37(48):736-747
(4) CHBUMED ltr 6220 ser 24/0204 of 26 Oct 90

1. Purpose. To establish policy in the areas of testing, notification, counseling, and retention related to the HTLV-I and II infection.

2. Background

a. HTLV-I is a human retrovirus found primarily in southwestern Japan (including Okinawa) and the Caribbean as well as parts of Central America, South America, and Africa. In the United States, the prevalence in the general population is low, between 2 to 5 per 10,000. Risk groups in the United States have been identified among persons from endemic areas, intravenous drug users, prostitutes, recipients of blood transfusions, and the sexual partners of persons in these risk groups.

(1) HTLV-I is a different retrovirus from the Human Immunodeficiency Virus Type 1 (HIV-1) which has been associated with the Acquired Immunodeficiency Syndrome (AIDS), and the Human Immunodeficiency Virus Type 2 (HIV-2), the cause of an AIDS-like illness in West Africa. HTLV-I does not cause AIDS. The presence of HTLV-I antibody does not imply infection with HIV-1 or HIV-2, or the risk of developing AIDS. The epidemiology of HTLV-I infection is different from that of HIV-1, in that sero-positivity to this virus is rare among homosexual men, patients in sexually transmitted disease clinics, and hemophiliacs.

0510-LD-056-4380

(2) HTLV-I is transmitted parenterally (via blood transfusion of cellular components or intravenous drug abuse), from mother to child (primarily through breast feeding), and through sexual contact. The efficiency of sexual transmission is unclear; however, it appears to be transmitted predominately from male to female.

(3) The HTLV-I virus is the etiologic agent of adult T-cell leukemia/lymphoma (ATLL) and a slowly progressive neurologic disorder called tropical spastic paraparesis/HTLV-I-Associated Myelopathy (TSP/HAM). The lifetime risk of an HTLV-I infected person developing one of these disorders is unknown; however, it is estimated to be 3 to 5 percent.

b. HTLV-II is another retrovirus similar in structure to HTLV-I (Note: HTLV-II is different from HIV-2). There is some cross-reaction between the HTLV-I and II viruses and highly specific confirmatory tests are needed to distinguish the two retroviruses. The clinical significance of HTLV-II is unknown at this time.

3. Military Importance. The primary concern to the active duty Navy and Marine Corps relating to HTLV-I and II is maintaining a pool of blood donors free of retroviruses. This includes the "walking blood bank" used in time of operational need where active members are selected to provide units of blood to wounded personnel when stores of banked blood are inadequate, depleted, or completely unavailable.

4. Testing and Notification Policy. Active duty personnel are not routinely screened for infection for HTLV-I and II infection. Military blood banks have been screening all units of donated blood for HTLV-I since March 1989. Personnel with HTLV-I or II infection are permanently barred from future blood donations. Enclosure (1) provides policies for testing, counseling, and notification. Enclosure (2) provides guidance for confirmatory testing for repeatedly reactive HTLV-I specimens. The U.S. Public Health Service guidelines for patient education concerning HTLV-I/II are in enclosure (3).

5. Clinical Evaluations. Personnel with HTLV-I/II infection do not routinely require a clinical evaluation at a Navy hospital designated as an HIV education center (as required for HIV infection in reference (a)). After personnel are notified of their test results, they will receive:

a. A physical examination with particular attention to the lymphatic and neurological examination.

b. A complete blood count with differential white blood count and careful examination of the peripheral blood smear looking for atypical white blood cells.

c. Counseling per enclosures (1) and (3). Further information can be provided from the nearest naval hospital with an internal medicine staff or the cognizant Navy environmental and preventive medicine unit.

6. Safety of the Blood Supply

a. Department of the Navy (DON) blood programs and civilian blood agencies collecting blood on naval installations must follow Armed Services Blood Program Office (ASBPO) policies, Food and Drug Administration (FDA) guidelines, and accreditation requirements of The American Association of Blood Banks (AABB).

b. If units of blood cannot be screened for infectious agents before transfusing (contingency or battlefield conditions), the ASBPO in coordination with military departments and unified/specified commands will provide guidance to operational units.

7. Retention Policy. There are no restrictions to retention or assignments based solely on serologic evidence of HTLV-I or II infection. Personnel with one of the late complications of HTLV-I or II infection listed in enclosure (3) may require a medical board determination for future service.

8. Reporting Requirements. Infection with HTLV-I or II is a reportable disease for active duty members to the Department of Defense Reportable Disease Data Base through the cognizant Navy environmental and preventive medicine unit as described in enclosure (4).

9. Forms

a. SF 600 (5-84), Chronological Record of Medical Care, NSN 7540-00-634-4176 and SF 513 (9-77), Consultation Sheet, NSN 7540-00-634-4127 are available from the Federal Supply System through normal supply procurement procedures.

b. DD 572 (6-90), Blood Donor Record, S/N 0102-LF-010-7400, is available from the Navy Supply System and may be requisitioned per NAVSUP P-2002D.

D. F. Hagen

D. F. HAGEN

Stocked:
Naval Publications and Forms Directorate
Physical Distribution Division Code 103
5801 Tabor Ave.
Phila., PA 19120-5099

HTLV I AND II INFECTION: TESTING, NOTIFICATION, AND COUNSELING POLICIES AND PROCEDURES

1. Background Information on HTLV-I and II Testing

a. On 11 November 1988, the ASBPO required all military blood banks to begin testing of all blood supplies for HTLV-I antibody, as soon as such tests were approved by the FDA. Three manufacturers were subsequently granted licenses on 29 November 1988 to manufacture and distribute HTLV-I test kits. No test kits have been approved for the detection of antibody to other retroviruses, such as HTLV-II.

b. On 29 November 1988, the FDA also recommended testing all donated blood for antibodies to HTLV-I with licensed enzyme immunoassay (EIA) tests and advised that all blood and cellular components determined to be potentially contaminated with HTLV-I be destroyed. Donors with repeatedly reactive screening tests for HTLV-I antibodies on more than one occasion were to be indefinitely deferred. Those with repeatedly reactive results were recommended to be permanently deferred if they are determined to have antibodies to HTLV-I or HTLV-II on confirmatory testing.

c. On 9 December 1988, enclosure (3) was published by the Centers for Disease Control. No additional guidance has been issued. This included a recommendation that HTLV-I infected persons be counseled by a health care professional.

d. An arrangement for confirmatory testing of blood for retroviruses has been made between the Division of Retrovirology, Walter Reed Army Institute of Research (WRAIR) and the military blood banks throughout the DoD.

2. Testing

a. Forward all donated units found to be HTLV-I antibody-positive by EIA to WRAIR for further analysis by Western Blot and other highly specific confirmatory tests for HTLV-I and HTLV-II. Enclosure (2) provides established procedures for shipping blood to WRAIR. A copy of the donor card and information on the total number of units tested by location must accompany each unit or blood component.

b. Any initial specimen confirmed by WRAIR to be HTLV-I or II antibody-positive and reported out as "consistent with HTLV-I or II infection" must be followed up with repeat testing to verify. The purpose of this verification testing is to substantiate the earlier findings by WRAIR, and to characterize the type of retroviral infection by the highly specific testing required to differentiate between HTLV-I and HTLV-II.

c. Blood specimens drawn for purposes of HTLV-I and II verification testing include: three green-top tubes of uncentrifuged blood, and sera from two large red-top tubes. Send these specimens unrefrigerated via overnight express delivery to the Division of Retrovirology, WRAIR, Suite 201, 13 Taft Court, Rockville, MD 20850. Specimens must be labeled with the patient's name, sponsor's social security number, and the date drawn. A laboratory slip with the address of the referring blood bank, a specific point of contact, and telephone number must be included. The shipment must be preceded by a telephone call to WRAIR's Department of Diagnostic Retrovirology, at (301) 295-6414/6415 or DSN 295-6414/6415, to ensure proper handling of the specimens. Results will be returned to the sending laboratory as soon as possible.

d. All specimens sent to WRAIR for confirmatory or verification testing will have an aliquot of sera frozen and saved at WRAIR for future reference, with a copy of the donor card kept on file.

e. In addition to testing done in the blood banks, hospitals with EIA testing capability will be prepared to perform additional screening for HTLV-I on request. Such requests could come from spouses or family members of HTLV-I or II infected patients or clinicians evaluating patients with suspected neurological disorders associated with these retroviruses. The WRAIR Division of Retrovirology is available for consultation regarding specific testing procedures.

f. Patients with HIV-1 or HIV-2 infection are not required to undergo additional separate testing for HTLV-I or II infection at this time.

g. There are no plans in the near future to add HTLV-I and II screening to the HIV force testing program for the military.

h. At this time, there are no requirements for mandatory or recommended testing for personnel traveling to or returning from geographical areas with a higher prevalence of HTLV-I or II infection.

i. The initial confirmatory test results for antibody-positive specimens will be reported by WRAIR to the referring blood bank as:

(1) "Negative for HTLV-I or II antibodies."

(2) "Consistent with HTLV-I or II infection."

A report stating "consistent with HTLV-I or II infection" implies the need for initial counseling and the drawing of additional blood samples to ascertain the type of retroviral infection.

3. Notification Procedures and Guidelines

a. Repeatedly Positive EIA Results. If WRAIR determines a specimen is "consistent with HTLV-I infection," the nearest preventive medicine department in partnership with the blood bank will arrange for appropriate counseling, if indicated, (see paragraph 4). Routine screening for HTLV-I of all units of blood donations will continue indefinitely, and repeatedly positive EIA results will be maintained by the DoD Reportable Disease Data Base (for active duty data only - see enclosure (3)) and by WRAIR (for all military health care beneficiaries).

b. Positive EIA Screening Test with a Negative Confirmatory Test, Based on a Single Sample. Donors with a single positive HTLV-I screening result (EIA test) and a negative confirmatory test based on this one blood sample will not be notified. Such individuals will be assumed to have a false positive screening test result. Their donated unit will have to be discarded, although they may donate at a later date.

c. Positive EIA Screening Test with Negative Confirmatory Tests, Based on Repeated Donations or Samples. Per FDA guidelines, donors who are repeatedly positive by the EIA test on separate donations or testing, but negative on confirmatory testing must be notified. These individuals will be told that their Positive test does not mean that they are infected with HTLV-I, HTLV-II, HIV-1, or any other recognized retroviruses, and probably indicates a false positive test. It should be explained that our current level of medical technology makes it difficult to attribute or attach any further significance to this test result. Inform them that they are "indefinitely deferred" from donating blood, as a precautionary measure recommended by the FDA. Such individuals do not require any special counseling, but should receive a written statement explaining their antibody test results and nondonor status. Document this notification in their medical record. Information must be handled in a confidential manner. These individuals will be reported to the DoD Reportable Disease Data Base per enclosure (3).

d. Positive on EIA Screening and Confirmatory Test. HTLV-I or II antibody-positive individuals (positive by confirmatory testing on a single sample) must be notified of their positive test result, and appropriately counseled. It is imperative to alleviate individual fears about the positive laboratory test result and reiterate and stress: "This is not an indication of HIV infection or AIDS."

(1) Notification and counseling procedures should be arranged in advance between the preventive medicine department and the pathology department responsible for the blood bank. Notification procedures must be initiated only after WRAIR has

completed confirmatory testing and definitely determined that the specimen is HTLV-I or II antibody-positive.

(2) The notification should be done in a similar fashion to notification for hepatitis B infection (hepatitis B surface antigen-positive individuals). A closely coordinated effort between laboratory and preventive medicine departments is critical. It must be emphasized that HTLV-I notification and counseling differs from that for HIV-1 infection. For example, the individual's commanding officer does not need to be informed of this result. Referral to a major naval hospital designated as an HIV evaluation center, that is required for HIV antibody-positive persons, is not required with HTLV-I or II notification.

(3) It is acceptable to notify the HTLV-I or II antibody-positive individual by registered letter. The letter should contain the following information:

(a) Results of the initial HTLV-I and II test.

(b) A brief explanation of the significance of test results.

(c) Additional verification testing, if indicated.

(d) Reassurance that a positive test result does not mean HIV-1 infection and AIDS.

(e) Notification of the deferred donor status.

(f) Need for counseling and further actions (no need to specify details during notification).

(g) Name, office, and telephone number of the command point of contact for further information, repeat testing, and counseling.

(4) Notification by telephone is not recommended, unless it is merely to inform an individual to come in to discuss a medical problem. Counseling should not be attempted over the telephone.

(5) If an HTLV-I or II antibody-positive donor has relocated to another area, the preventive medicine department at the original medical treatment facility (MTF) will notify the preventive medicine department head at the MTF nearest to where the individual has relocated. If the individual has left the military or cannot be located, such information will be referred to the cognizant Navy environmental and preventive medicine unit.

e. Indeterminant Confirmatory Test Results. Sometimes, even after confirmatory testing and submitting additional specimens,

it may not be possible to determine the status or type of retroviral infection. Individuals will be advised to be refrain from donating blood and be retested in 6 months. In such an event, the Division of Retrovirology at WRAIR will provide specific guidance to the blood bank and the preventive medicine department on appropriate steps to take.

f. Civilians Identified as HTLV-I or II Antibody-Positive. Civilian health care beneficiaries, such as family members and retirees, will be referred for notification and counseling within the military health care system. Civilian nonbeneficiaries identified through routine testing of donated blood collected on military installations will be referred to their private physicians for counseling and follow-up. Currently, no States require HTLV-I or II reporting and counseling.

g. Civilian Blood Collection Agencies. On 17 April 1989, the ASBPO required civilian blood collection agencies on military installations to:

(1) Notify donors of a confirmed positive or two subsequent repeated reactive HTLV-I or II result.

(2) Advise the donors that medical counseling is available through the military health care system.

(3) Report confirmed positive and repeatedly reactive HTLV-I and II results on military donors to a point of contact designated by the commanding officer of the nearest MTF.

h. Look Back for HTLV-I and II. Look back (tracing of recipients of units of blood from an infected donor) for HTLV-I and II is required by the AABB, "To the extent that records permit." All blood donors identified with a repeatedly reactive HTLV-I or II result must be asked about donation history (dates, locations, etc.). This information must be forwarded to the Navy blood program office for HTLV-I and II look back studies as designated by ASBPO policy and guidance.

4. Counseling Procedures and Guidelines

a. Counseling of patients or donors for HTLV-I or HTLV-II infection will ordinarily be the responsibility of preventive medicine departments. Notification by the local blood bank should precede counseling. Counseling at each MTF may vary and can be performed by an infectious disease or other internal medicine specialist, preventive medicine officer, or other health care professional who is familiar with retroviral infections and is properly trained in counseling. The MTF commanding officer or officer in charge will designate the point of contact for HTLV-I and II at that command. Additional information is available at

naval hospitals with infectious disease specialists and the Navy environmental and preventive medicine units.

b. Counseling must be conducted in a confidential manner. The donor must be provided information on what is known about HTLV-I and II infection. The U.S. Public Health Service guidance in enclosure (3) may be used to counsel patients and be distributed as a patient education handout.

c. Specific aspects pertaining to transmission and the significance of test results should be emphasized. Additional points of emphasis are that HTLV-I and II does not cause AIDS, and the positive blood test does not imply infection with HIV-1.

d. The patient will be given an opportunity to ask questions. If an individual was identified through blood donation, explain that testing is a result of requirements established by the FDA and they are now permanently ineligible to donate blood. Women should be counseled not to breast-feed children. Both men and women should be advised not to donate organs, tissues, or sperm, since little is known about the potential for transmission through other body fluids and tissues.

e. It must be made explicitly clear to military members who are HTLV-I or HTLV-II antibody-positive that special rules pertaining to HIV-infected members do not apply to them. Specifically, they remain in a deployable status and they are eligible for special schooling, promotion, or specific unit assignments, including overseas assignments and their service records will not be marked identifying them as HTLV-I or II infected. A medical board will be processed only if the HTLV-I or II member demonstrates the rare sequelae of this virus such as ATLL or TSP/HAM.

f. Since little is known about HTLV-I or HTLV-II infection, individuals who are identified as seropositive must be advised to have family members tested also. These members must be counseled similarly if they are found to be antibody-positive. Spouses of HTLV-infected individuals must be tested on an annual or biennial basis to determine if seroconversion has or has not occurred.

g. Questions will inevitably arise about the potential for sexual transmission. Patients must be informed that based on the limited information available, sexual transmission appears to be relatively inefficient, but male to female transmission may pose a somewhat greater risk than female to male transmission. Condoms probably provide some protection.

h. HTLV-I or II infected nursing mothers must be discouraged from breast-feeding.

i. The risk of transmission with intravenous drug abuse and the sharing of drug paraphernalia, including needles and syringes, must be discussed during the counseling session.

j. A note documenting counseling must be entered in the patient's health care record on a SF 600 (Chronological Record of Medical Care) or SF 513 (Consultation Sheet).

k. HTLV-I and II infected health care beneficiaries must be informed that a confidential list of persons identified with this infection is maintained in the DoD Reportable Disease Data Base and by WRAIR (see enclosure (3)). This data base is being maintained should there be a need to contact such persons in the future with new information on diagnosis, treatment, or prevention.

l. As a part of the counseling, provide a name and telephone number of a medical point of contact locally whom they may contact for additional information, advice, or support.

GUIDELINES FOR REPEATEDLY REACTIVE HTLV-I SPECIMENS

1. Forward all repeatedly reactive HTLV-I specimens and plasma components to a centralized confirmatory facility at WRAIR except for locations outside of the continental United States (OCONUS). OCONUS facilities may submit specimens only.

2. WRAIR will be responsible for confirmatory assays to include western blots, radioimmunoprecipitation assays (RIPA) and a recombinant procedure. As required, additional specimens will be requested by WRAIR for further confirmation.

3. Blood banks will ship the unit of plasma, any extra specimens in provials, and platelet concentrate (if it was prepared) from the donor who is repeatedly reactive. The units of plasma and platelet concentrate will be labeled "For Laboratory Research Purposes Only," per ASBPO guidelines. These components will be packed in triple containers with sufficient absorbent material to absorb spillage if leakage should occur. Label outer container with etiologic agent label. Do not ship in the standard DoD blood shipping box.

4. The plasma components will not require the use of wet or dry ice. Ship at ambient temperature but ensure overnight delivery by an air courier service with door-to-door delivery during normal duty hours Monday through Friday. Note: OCONUS may ship only sera or plasma in cryogenic specimen tubes.

5. The shipping facility will provide a point of contact, telephone number, and complete MTF address.

6. The shipping facility will include a copy of the donor care record (DD 572) in the shipment.

7. The shipping facility must call the Chief, Department of Diagnostic Retrovirology at WRAIR in advance of shipment and provide necessary instructions of pending shipment. The telephone number is (301) 295-6410/6411 or DSN 295-6410/6411.

8. Ship prepaid to:

Walter Reed Army Institute of Research
<u>Attn</u>: Chief, Department of Diagnostic Retrovirology
Division of Retrovirology
Suite 201
13 Taft Court
Rockville, MD 20850

Current Trends

Licensure of Screening Tests for Antibody to Human T-Lymphotropic Virus Type I

Screening tests for antibody to human T-lymphotropic virus type I (HTLV-I), the first-recognized human retrovirus, have been licensed by the Food and Drug Administration (FDA). These tests have been recommended by the FDA for screening of blood and cellular components donated for transfusion. They have also been approved as diagnostic tests, which may be useful in evaluating patients with clinical diagnoses of adult T-cell leukemia/lymphoma (ATL) and tropical spastic paraparesis (TSP)/HTLV-I–associated myelopathy (HAM), both of which have been associated with HTLV-I infection. Because licensure will probably result in widespread use of these tests, the information presented below is provided for physicians and public health officials who may need to interpret HTLV-I test results and to counsel persons whose serum specimens are reactive in these tests. **Users of the new HTLV-I screening tests are cautioned that additional, more specific tests are necessary to confirm that serum specimens that are repeatably reactive in these screening tests are truly positive for HTLV-I antibody.** Users should also be aware that neither the screening tests nor more specific tests can distinguish between antibody to HTLV-I and antibody to the closely related human retrovirus, human T-lymphotropic virus type II (HTLV-II).

HTLV-I does not cause AIDS, and the finding of HTLV-I antibody in human blood does not imply infection with human immunodeficiency virus (HIV) or a risk of developing acquired immunodeficiency syndrome (AIDS).

BACKGROUND: HTLV-I

HTLV-I was isolated in 1978 and first reported in 1980 (*1*). Although a member of the family of retroviruses, HTLV-I is *not* closely related to HIV, the virus that causes AIDS. HTLV-I does not cause depletion of T-helper lymphocytes, and it is not generally associated with immunosuppression.

Screening Tests — Continued

HTLV-I differs from HIV in its morphologic and genetic structure and in that HTLV-I antigens should not cross-react with the antigens of HIV. The HTLV-I genome contains four major genes: *gag*, which encodes core proteins of 15,000 (p15), 19,000 (p19), and 24,000 (p24) daltons; *pol*, which encodes a polymerase (reverse transcriptase) protein of 96,000 daltons; *env*, which encodes envelope glycoproteins of 21,000 (gp21) and 46,000 (gp46) daltons; and *tax*, which encodes a transactivator protein of 40,000 daltons (p40x).

Seroprevalence

HTLV-I infection is endemic primarily in southwestern Japan, the Caribbean, and some areas of Africa (*2*). Seroprevalence in well-characterized areas appears to increase with patient age, with rates in females markedly higher than those in males beginning in the 20–30-year age range. Seroprevalence rates as high as 15% in the general population and 30% in older age groups have been reported in some areas of Japan (*3*). In the Caribbean islands, rates may be as high as 5% in the general population and 15% in older age groups (*4*).

In the United States, HTLV-I infection has been identified mainly in intravenous-drug users (IVDUs), with seroprevalence rates ranging from 7% to 49% (*5,6*). Elevated rates have also been reported in female prostitutes (in whom IV-drug use is a major risk factor) (*7*) and in recipients of multiple blood transfusions (*8*). Seropositivity is rare among homosexual men and among patients in sexually transmitted disease clinics (*9,10*), and it appears to be nonexistent in hemophilic men without other risk factors (*11*). Systematic determination of HTLV-I seroprevalence in the general population of the United States has not been undertaken. However, in a study of 39,898 random blood donors in eight U.S. cities, 10 (0.025%) were seropositive for HTLV-I (*12*).

Transmission

Transmission of HTLV-I infection by blood transfusion is well documented in Japan, with a seroconversion rate of 63% in recipients of the *cellular* components of contaminated units (whole blood, red blood cells, and platelets) (*13*). Transmission by the plasma fraction of contaminated units has not resulted in infection; this finding has been attributed to the fact that HTLV-I is highly cell-associated. Transmission among IVDUs is presumed to occur by sharing of needles and syringes contaminated with infectious blood.

Transmission from mother to child occurs through breastfeeding; breastfed infants of seropositive mothers have an approximately 25% probability of becoming infected (*14*). However, infection has also occurred in infants who are not breastfed, suggesting that intrauterine and/or perinatal transmission may occur.

Sexual transmission of HTLV-I appears to be relatively inefficient (*15*). Transmission from male to female, however, appears to be more efficient than from female to male (*16*).

Disease Associations

HTLV-I has been etiologically associated with adult T-cell leukemia/lymphoma (ATL), a malignancy of mature T-lymphocytes characterized by skin lesions, visceral involvement, circulating abnormal lymphocytes, hypercalcemia, and lytic bone lesions (*17*). ATL has been recognized in Japan, the Caribbean, and Africa. No systematic attempt has been made to record cases of ATL in the United States, but 74 cases were reported to the National Institutes of Health between 1980 and 1987 (*18*). Approximately half of these cases occurred in persons of Japanese or Caribbean

Screening Tests — Continued

ancestry; most of the remainder were in blacks from the southeastern United States. ATL tends to occur equally in men and women, with peak occurrence in persons 40–60 years of age.

It is thought that a person must be infected with HTLV-I for years to decades before ATL develops. The lifetime risk of ATL among HTLV-I–infected persons has been estimated to be approximately 2% in two studies in Japan (*19,20*). In Jamaica, the lifetime risk of ATL among persons infected before the age of 20 years was estimated to be 4% (*21*).

Because of the long latent period of ATL, the risk of this disease among persons infected by blood transfusion (many of whom are elderly and may not survive their underlying disease) is not thought to be substantial. In fact, no cases of ATL associated with blood transfusion have been reported.

HTLV-I has also been associated with a degenerative neurologic disease known as tropical spastic paraparesis (TSP) in the Caribbean and as HTLV-I–associated myelopathy (HAM) in Japan (*22,23*). TSP/HAM is characterized by progressive difficulty in walking, lower extremity weakness, sensory disturbances, and urinary incontinence. Although most cases have been reported from countries in which HTLV-I is endemic, a few cases have occurred in the United States (*24*). TSP/HAM occurs in persons of all age groups, with peak occurence in ages 40–49 years. Rates are higher in females than in males. The lifetime risk of TSP/HAM among persons infected with HTLV-I is unknown but appears to be very low. The latent period for this disease appears to be less than for ATL, and the disease probably can be caused by blood transfusion. Of 420 Japanese patients with HAM from whom information was available, 109 (26%) gave a history of blood transfusion; the mean interval between transfusion and onset of neurologic symptoms was estimated to be 4 years (M. Osame, unpublished data).

HTLV-I does not cause AIDS, and the finding of HTLV-I antibody in human blood does not imply infection with HIV or a risk of developing AIDS.

BACKGROUND: HTLV-II

HTLV-II is closely related to HTLV-I. The genome of HTLV-II encodes viral proteins that are similar to those of HTLV-I, and there is extensive serologic cross-reactivity among proteins from HTLV-I and HTLV-II.

No specific information is available regarding the seroepidemiology or the modes of transmission of HTLV-II. There is some evidence that some of the HTLV-I seropositivity in the United States, especially in IVDUs, may be caused by HTLV-II (*5*).

Two cases of disease have been associated with HTLV-II infection. HTLV-II was first isolated from a patient with a rare T-lymphocytic hairy cell leukemia (*25*). In the second case, HTLV-II was isolated from a patient who had the more common B-lymphocytic form of hairy cell leukemia and who also suffered from a T-suppressor lymphoproliferative disease (*26*). No serologic evidence of HTLV-II infection has been found in 21 additional cases of hairy cell leukemia (*27*). Thus, the disease associations of HTLV-II are unclear, and nothing is known regarding lifetime risk of disease among infected persons.

SEROLOGIC TESTS FOR HTLV-I

Interpretation

The screening tests that have been licensed by the FDA are enzyme immunoassays (EIAs) to detect HTLV-I antibody in human serum or plasma. Specimens with absorbance values greater than or equal to the cutoff value determined by the

Screening Tests — Continued

manufacturer are defined as initially reactive. Initially reactive specimens must be retested in duplicate to minimize the chance that reactivity is due to technical error. Specimens that are reactive in either of the duplicate tests are considered repeatably reactive. Specimens that do not react in either of the duplicate repeat tests are considered nonreactive. **Additional, more specific serologic tests are necessary to confirm that serum specimens repeatably reactive in the screening tests are positive for HTLV-I antibody. Users of the screening tests must have available to them additional, more specific tests to properly interpret repeatably reactive screening tests.** Such tests are available in research institutions, industry, and some diagnostic laboratories. No such tests have been licensed by the FDA.

Tests used to confirm HTLV-I seropositivity must be inherently capable of identifying antibody to the core (*gag*) and envelope (*env*) proteins of HTLV-I. (The immunoreactivities of the polymerase [*pol*] and transactivator [*tax*] proteins of HTLV-I have not been well-defined in current test systems.) Specific tests include Western immunoblot (WIB) and radioimmunoprecipitation assay (RIPA). Indirect fluorescent antibody (IFA) testing for HTLV-I has been used in some laboratories, but IFA does not detect antibody to specific HTLV-I gene products.

WIB appears to be the most sensitive of the more specific tests for antibody to *gag* protein products p19, p24, and (*gag*-derived) p28, whereas RIPA appears to be most sensitive for antibody to the *env* glycoproteins gp46 and (*env* precursor) gp61/68. Based on experience with these tests in several laboratories, the following confirmatory criteria for HTLV-I seropositivity have been adopted by the Public Health Service Working Group: a specimen must demonstrate immunoreactivity to the *gag* gene product p24 **and** to an *env* gene product (gp46 and/or gp61/68) to be considered "positive." Serum specimens not satisfying these criteria but having immunoreactivities to at least one suspected HTLV-I gene product (such as p19 only, p19 and p28, or p19 and *env*) are designated "indeterminate." Serum specimens with no immunoreactivity to any HTLV-I gene products in additional, more specific tests are designated "negative." **Both WIB and RIPA may be required to determine whether a serum specimen is positive, indeterminate, or negative.**

Although additional, more specific tests have been somewhat standardized, the quantities and the molecular weights of HTLV-I proteins produced by various cell lines vary considerably. Hence, the cell of origin for HTLV-I antigens used in either WIB or RIPA, as well as the method of antigen preparation, may markedly influence test sensitivity and interpretation of immunoreactivity against individual HTLV-I proteins. Laboratories performing these tests, however, should be able to detect antibody to the *gag* and *env* gene products of HTLV-I in WIB and/or RIPA.

Sensitivity, Specificity, and Predictive Value

Using the WIB and RIPA available in research laboratories and the confirmatory criteria described above to define the presence of HTLV-I antibody, the sensitivities of the three EIAs that have been licensed by the FDA have been estimated from the performance of the tests on a reference panel of 137 antibody-positive serum specimens. All three EIAs were repeatably reactive for 137 of 137 panel serum specimens, yielding an estimated sensitivity of 97.3%–100% by the binomial distribution at 95% confidence. Specificity* of the EIAs was estimated for each test from

*Specificity was calculated as follows: (total donations screened minus total number repeatably reactive in EIA) divided by (total donations screened minus number confirmed as positive by additional testing).

Screening Tests — Continued

screening of at least 5000 normal U.S. blood donors in nonendemic areas. Estimated specificities ranged from 99.3% to 99.9% by the binomial distribution at 95% confidence. However, a specificity >99% but <100% may still yield a low positive predictive value when the screening test is used in a low-prevalence population. For example, in the study of U.S. blood donors cited above, 68 donors were repeat reactors in the screening test, but only 10 (15%) were determined to be HTLV-I–seropositive in more specific testing. This relatively low positive predictive value emphasizes the need for additional, more specific testing of specimens repeatably reactive in the EIA.

Neither the EIAs nor the additional, more specific tests can distinguish between antibodies to HTLV-I and HTLV-II. More sophisticated techniques, such as virus isolation and gene amplification (polymerase chain reaction [PCR]) are required to differentiate HTLV-I from HTLV-II infection.

(Continued on page 745)

Screening Tests — Continued

USE OF HTLV-I SCREENING TESTS IN BLOOD BANKS

The FDA recommends that whole blood and cellular components donated for transfusion be screened for HTLV-I antibody using a licensed EIA screening test. The FDA further recommends that units that are repeatably reactive by EIA be quarantined, then destroyed, unless otherwise stipulated by the FDA. Source plasma (obtained from plasma donors) intended for use in further manufacturing need not be screened for HTLV-I antibody.

DONOR DEFERRAL AND NOTIFICATION

FDA recommends permanent deferral of donors whose sera are repeatably reactive in EIA and confirmed as positive for HTLV-I antibody by additional, more specific testing. Such donors should be notified and counseled accordingly.

Donors whose serum specimens are repeatably reactive in the EIA but not confirmed as positive for HTLV-I antibody need not be notified on the first occasion. Although the donated units must be destroyed, the donors remain eligible for future donation. If, however, the donors test repeatably reactive in the EIA on a subsequent donation, they should be deferred indefinitely as donors and notified and counseled accordingly.

GUIDELINES FOR COUNSELING

Counseling should be considered a routine adjunct depending on the results of HTLV-I testing. Given some of the uncertainties related to testing, e.g., the inability to distinguish between antibodies to HTLV-I and HTLV-II, and the low probability that disease will occur in seropositive persons, every effort should be made to minimize the anxiety provoked by a repeatably reactive screening test, particularly one that is not confirmed as HTLV-I–seropositive by additional testing.

Persons confirmed as seropositive for HTLV-I should be notified that they have antibody to HTLV-I and are likely infected with HTLV-I or HTLV-II. They should be given information concerning disease associations and possible modes of transmission. In addition, they should be advised that they have been permanently deferred as blood donors and should neither give blood for transfusion nor share needles that have been used for percutaneous injection or infusions with other persons. Breastfeeding of infants should be discouraged. The paucity of data concerning sexual transmission of HTLV-I/HTLV-II does not permit a firm recommendation concerning sex practices; specific recommendations, such as the use of condoms to reduce the potential risk of sexual transmission, should be developed in consultation with a health-care professional.

Persons whose serum specimens are repeatably reactive on more than one occasion in the EIA but not confirmed as positive for HTLV-I antibody in more specific testing should be informed that they have inconclusive test results that do not necessarily imply infection with HTLV-I or HTLV-II. Nevertheless, they should be notified that they have been deferred indefinitely as donors and should not donate blood for transfusion. Periodic follow-up of such donors with EIA, more specific serologic tests, and possibly sophisticated techniques such as virus isolation and/or PCR may provide more reliable information regarding the presence of viral infection.

Reported by: Public Health Service Working Group.[†]

[†]D Anderson, MD, J Epstein, MD, L Pierik, J Solomon, PhD, Food and Drug Administration. W Blattner, MD, C Saxinger, PhD, National Cancer Institute; H Alter, MD, H Klein, MD, Clinical Center; P McCurdy, MD, G Nemo, MD, National Heart, Lung, and Blood Institute, National Institutes of Health. J Kaplan, MD, J Allen, MD, R Khabbaz, MD, M Lairmore, PhD, CDC.

Screening Tests — Continued

References

1. Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci USA 1980;77:7415–9.
2. Blattner WA. Retroviruses. In: AS Evans, ed. Viral infections of humans: epidemiology and control. 3rd ed. New York: Plenum, 1989 (in press).
3. Hinuma Y, Komoda H, Chosa T, et al. Antibodies to adult T-cell leukemia-virus–associated antigen (ATLA) in sera from patients with ATL and controls in Japan: a nation-wide sero-epidemiologic study. Int J Cancer 1982;29:631–5.
4. Clark JW, Saxinger C, Gibbs WN, et al. Seroepidemiologic studies of human T-cell leukemia/lymphoma virus type I in Jamaica. Int J Cancer 1985;36:37–41.
5. Robert-Guroff M, Weiss SH, Giron JA, et al. Prevalence of antibodies to HTLV-I, -II, and -III in intravenous drug abusers from an AIDS endemic region. JAMA 1986;255:3133–7.
6. Weiss SH, Ginzburg HM, Saxinger WC, et al. Emerging high rates of human T-cell lymphotropic virus type I (HTLV-I) and HIV infection among U.S. drug abusers [Abstract]. III International Conference on AIDS. Washington, DC, June 1–5, 1987:211.
7. Khabbaz RF, Darrow WW, Lairmore M, et al. Prevalence of antibody to HTLV-I among 1415 female prostitutes in the United States [Abstract]. IV International Conference on AIDS. Book 1. Stockholm, June 12–16, 1988:270.
8. Minamoto GY, Gold JWM, Scheinberg DA, et al. Infection with human T-cell leukemia virus type I in patients with leukemia. N Engl J Med 1988;318:219–22.
9. Manns A, Obrams I, Detels R, et al. Seroprevalence of human T-cell lymphotropic virus type I among homosexual men in the United States. N Engl J Med 1988;319:516–7.
10. Wiktor S, Cannon RO, Atkinson WA, Blattner WA, Quinn TH. Parenteral drug use is associated with HTLV-I and HIV infection among patients attending sexually transmitted disease (STD) clinics [Abstract]. IV International Conference on AIDS. Book 2.Stockholm, June 12–16, 1988:191.
11. Jason JM, Lairmore M, Hartley T, Evatt BL. Absence of HTLV-I coinfection in HIV-infected hemophilic men [Abstract]. 28th Interscience Conference on Antimicrobial Agents and Chemotherapy, Los Angeles, California, October 23–26, 1988:302.
12. Williams AE, Fang CT, Slamon DJ, et al. Seroprevalence and epidemiological correlates of HTLV-I infection in U.S. blood donors. Science 1988:240:643–6.
13. Okochi K, Sato H, Hinuma Y. A retrospective study on transmission of adult T cell leukemia virus by blood transfusion: seroconversion in recipients. Vox Sang 1984;46:245–53.
14. Sugiyama H, Doi H, Yamaguchi K, Tsuji Y, Miyamoto T, Hino S. Significance of postnatal mother-to-child transmission of human T-lymphotropic virus type-I on the development of adult T-cell leukemia/lymphoma. J Med Virol 1986;20:253–60.
15. Bartholomew C, Saxinger WC, Clark JW, et al. Transmission of HTLV-I and HIV among homosexual men in Trinidad. JAMA 1987;257:2604–8.
16. Kajiyama W, Kashiwagi S, Ikematsu H, Hayashi J, Nomura H, Okochi K. Intrafamilial transmission of adult T cell leukemia virus. J Infect Dis 1986;154:851–7.
17. Kuefler PR, Bunn PA Jr. Adult T cell leukaemia/lymphoma. Clin Haematol 1986;15:695–726.
18. Levine PH, Jaffe ES, Manns A, Murphy EL, Clark J, Blattner WA. Human T-cell lymphotropic virus type I and adult T-cell leukemia/lymphoma outside of Japan and the Caribbean basin. Yale J Biol Med (in press).
19. Tajima K, Kuroishi T. Estimation of rate of incidence of ATL among ATLV (HTLV-I) carriers in Kyushu, Japan. Jpn J Clin Oncol 1985;15:423–430.
20. Kondo T, Nonaka H, Miyamoto N, et al. Incidence of adult T-cell leukemia-lymphoma and its familial clustering. Int J Cancer 1985;35:749–51.
21. Murphy EL, Hanchard B, Figueroa JP, et al. Modeling the risk of adult T-cell leukemia/lymphoma (ATL) in persons infected with human T-lymphotropic virus type I. Int J Cancer (in press).
22. Gessain A, Barin F, Vernant JC, et al. Antibodies to human T-lymphotropic virus type-I in patients with tropical spastic paraparesis. Lancet 1985;2:407–10.
23. Osame M, Usuku K, Izumo S, et al. HTLV-I associated myelopathy, a new clinical entity. Lancet 1986;1:1031–2.
24. Bhagavati S, Ehrlich G, Kula RW, et al. Detection of human T-cell lymphoma/leukemia virus type I DNA and antigen in spinal fluid and blood of patients with chronic progressive myelopathy. N Engl J Med 1988;318:1141–7.

Screening Tests — Continued

25. Kalyanaraman VS, Sarngadharan MG, Robert-Guroff M, et al. A new subtype of human T-cell leukemia virus (HTLV-II) associated with a T-cell variant of hairy cell leukemia. Science 1982;218:571–3.
26. Rosenblatt JD, Golde DW, Wachsman W, et al. A second isolate of HTLV-II associated with atypical hairy-cell leukemia. N Engl J Med 1986;315:372–7.
27. Rosenblatt JD, Gasson JC, Glaspy J, et al. Relationship between human T-cell leukemia virus-II and atypical hairy cell leukemia: a serologic study of hairy cell leukemia patients. Leukemia 1987;1:397–401.

DEPARTMENT OF THE NAVY
BUREAU OF MEDICINE AND SURGERY
WASHINGTON, D.C. 20372-5120

IN REPLY REFER TO
6220
Ser 24/0204
26 Oct 90

From: Chief, Bureau of Medicine and Surgery

Subj: REPORTING OF LABORATORY TEST RESULTS FOR HEPATITIS B SURFACE ANTIGEN, MALARIA, AND HTLV-I/II

Ref: (a) OASD/HA memo, Additions to the Reportable Disease Data Base of 13 Jun 90
(b) NAVMEDCOMINST 6220.2A

Encl: (1) Laboratory Test Result Report (example)

1. Reference (a) requires all military services to report selected laboratory test results on active duty members to the Defense Manpower Data Center (DMDC) for addition to the Department of Defense Reportable Disease Data Base (RDDB). Currently, the RDDB contains human immunodeficiency virus (HIV) serologic test results for the total force.

2. Effective immediately, commanding officers of all medical treatment facilities (MTFs) must report positive laboratory tests for hepatitis B surface antigen (HBsAg), malaria parasites, and human T-lymphotropic virus type I and/or type II (HTLV-I/II) from all clinical and blood program laboratories. Guidelines for reporting include:

a. Report the results of tests conducted in the MTF laboratory, and report the results of tests which are sent to another laboratory (commercial, other civilian, or other military) for analysis but for which the MTF retains the responsibility to report the results to a healthcare provider. Commanding officers are encouraged to consolidate reporting for all laboratories under their control and to submit a single report, if practicable.

b. Report only the test results for active duty members of any of the military services; do not report results for other medical beneficiaries.

c. Report only positive results; do not report negative test results. Reports for HTLV-I and/or HTLV-II should be reported only if repeatedly (at least two times) positive on ELISA testing.

d. For each test result, report the patient's name, social security number, service, date of birth, date sample was collected, type of specimen (e.g., clinical or blood program), and test result. Enclosure (1) provides a suggested reporting format and the coding scheme for the data elements.

Subj: REPORTING OF LABORATORY TEST RESULTS FOR HEPATITIS B SURFACE ANTIGEN, MALARIA, AND HTLV-I/II

e. Duplicate reports on a given patient are expected because of repeat testing either during a hospitalization (e.g., serial malaria smears) or during followup care (e.g., HBsAg screen at six months to determine carrier status). Do not attempt to exclude duplicate reports. Report all positive test results.

3. Each MTF must submit a monthly report which includes all positive tests reported out of the MTF laboratory during the calendar month. Send reports to the cognizant Navy environmental and preventive medicine unit (NAVENPVNTMEDU), with a copy to the Navy Environmental Health Center (NAVENVIRHLTHCEN). Reports may be sent by message, NAVGRAM, letter, or facsimilie to arrive no later than the eighth day of the subsequent month. The first report is due no later than 8 November 1990 for test results reported out of the laboratory during the period 1-31 October 1990. Negative reports are required.

4. This laboratory reporting requirement does not replace or alter requirements of reference (b) to submit Disease Alert Reports (DARs) for cases of communicable disease. Nor does it replace any state or territorial requirements for laboratory reporting of diseases of public health importance. This reporting requirement should not supplant any command procedures for notifying healthcare providers and preventive medicine personnel of test results, or for ensuring that appropriate and timely preventive medicine action is taken.

5. NAVENPVNTMEDUs must monitor reports from MTFs in their area of cognizance to ensure that reports are complete and timely. As appropriate, laboratory reports will be used for communicable disease surveillance and to supplement disease information reported by DAR. NAVENPVNTMEDUs will report to the NAVENVIR-HLTHCEN any positive results on malaria smears, which operational units submitted for analysis per reference (b).

6. NAVENVIRHLTHCEN must maintain laboratory reports in a database and provide the data to DMDC by 15 January, 15 April, 15 July, and 15 October for each preceding quarter. The first report is due 15 January 1991.

7. Directions in this letter remain in effect until incorporated into a directive, or until modified or canceled.

8. Point of contact (POC) at this bureau is Captain W. F. Bina III, MC, USN, Director, Occupational Health and Preventive Medicine Division (MED-24), AUTOVON 294-1788 or (202) 653-1788. POC at NAVENVIRHLTHCEN is Commander D. H. Trump, MC, USN, Head, Epidemiology Department (NEHC-36), AUTOVON 564-7575 or

Subj: REPORTING OF LABORATORY TEST RESULTS FOR HEPATITIS B SURFACE ANTIGEN, MALARIA, AND HTLV-I/II

(804) 444-7575, extension 228. Point of contact at the cognizant NAVENPVNTMEDU is the Epidemiology Department.

W. A. BUCKENDORF
Assistant Chief for Fleet
Readiness and Support

Distribution:
SNDL
FA47 (NAVHOSP)
FA49 (NAVMEDCLINIC)
FB58 (NAVHOSP)
FB60 (NAVMEDCLINIC)
FC16 (NAVMEDCLINIC)
FC17 (NAVHOSP)
FT108 (NAVHOSP)
FT110 (NAVMEDCLINIC)
FW1 (NATNAVMEDCEN)
FW3 (NAVHOSP)
FW4 (NAVMEDCLINIC)
FH15 (NAVENPVNTMEDU)
FH26 (NAVENVIRHLTHCEN)

Copy to:
OASD/HA Washington DC
NAVMEDRSCHDEVCOM Bethesda MD
SFMC San Francisco CA
HLTHCARE SUPPO Barbers Point HI
HLTHCARE SUPPO Jacksonville FL
HLTHCARE SUPPO London UK
HLTHCARE SUPPO Norfolk VA
HLTHCARE SUPPO San Diego CA
MEDDEN AFFAIRS Great Lakes IL

LABORATORY TEST RESULT REPORT (EXAMPLE)

From: Commanding Officer
To: Officer in Charge, Navy Environmental and Preventive Medicine Unit No. #, (Attn: Epidemiology Department)

Subj: LABORATORY TEST RESULTS MONTHLY REPORT

Ref: (a) BUMED ltr 6220 Ser _____ of __ Oct 1990

1. Per reference (a), laboratory results for the period 1-31 October 1990 are:

SSN	LName	FI	Svc	DOB	ICD	Source	DOT
xxxxxxxxx	xxxxxxx	x	x	yymmdd	xxxx	x	yymmdd
.							
xxxxxxxxx	xxxxxxx	x	x	yymmdd	xxxx	x	yymmdd

2. Point of contact at this command is LT I. M. Able, MSC, USN, AUTOVON xxx-xxxx, commercial xxx-xxx-xxxx.

I. M. ABLE
By direction

Copy to:
NAVENVIRHLTHCEN (NEHC-36) Norfolk VA

==========

ADDRESSES AND PLADS

Navy Environmental and Preventive Medicine Unit No. 2
Naval Station
Norfolk, VA 23511-6288
NAVENPVNTMEDU TWO NORFOLK VA

Navy Environmental and Preventive Medicine Unit No. 5
Naval Station, Box 143
San Diego, CA 92136-5143
NAVENPVNTMEDU FIVE SAN DIEGO CA

Navy Environmental and Preventive Medicine Unit No. 6
Box 112
Pearl Harbor, HI 96860-5040
NAVENPVNTMEDU SIX PEARL HARBOR HI

Navy Environmental and Preventive Medicine Unit No. 7
Box 41
FPO New York 09521-4200
NAVENPVNTMEDU SEVEN NAPLES IT

Navy Environmental Health Center
2510 Walmer Avenue
Norfolk, VA 23513-2617
NAVENVIRHLTHCEN NORFOLK VA//36//

Enclosure (1)

CODING SCHEME FOR DATA ELEMENTS

SSN = Social security number (9 digits)

LName = First seven characters of last name

FI = First initial

Svc = Military service

Enter: N for Navy
M for Marine Corps
F for Air Force
A for Army
O for Other

DOB = Date of birth (year, month, day)

ICD = Test result, coded by International Classification of Diseases code

Enter: 0840 for Plasmodium falciparum on malaria smear
0841 for P. vivax on malaria smear
0842 for P. malariae on malaria smear
0843 for P. ovale on malaria smear
0845 for mixed malaria infection
0846 for unknown malaria species

V026 for hepatitis B surface antigen positive

V029 for repeatedly reactive on HTLV-I/II testing

S = Source or indication for testing

Enter: I for clinically indicated
B for blood donor
R for requested by individual
O for obstetrics clinic screening
X for any other source

DOT = Date sample was collected (year, month, day)