SCREENING FOR ANTI-HTLV-III IN MILITARY PERSONNEL

T H E S I S

Submitted In Partial Fulfilment For

Master Degree

In

Clinical Pathology

By

Erfan Mohamed Abu El Fotoh

Supervised by

Prof. Dr: Samir Hanna

Prof. And Head Of
Clinical Pathology
Department
Ain Shams University

Prof. Dr: Ali Rashed

Head Of Educational
Affairs
Medical Military
Academy

Dr: Mona Rafik

Lecturer Of
Clinical Pathology
Ain Shams University

Faculty Of Medicine
Ain Shams University

1986

A C K N O W L E D G E M E N T

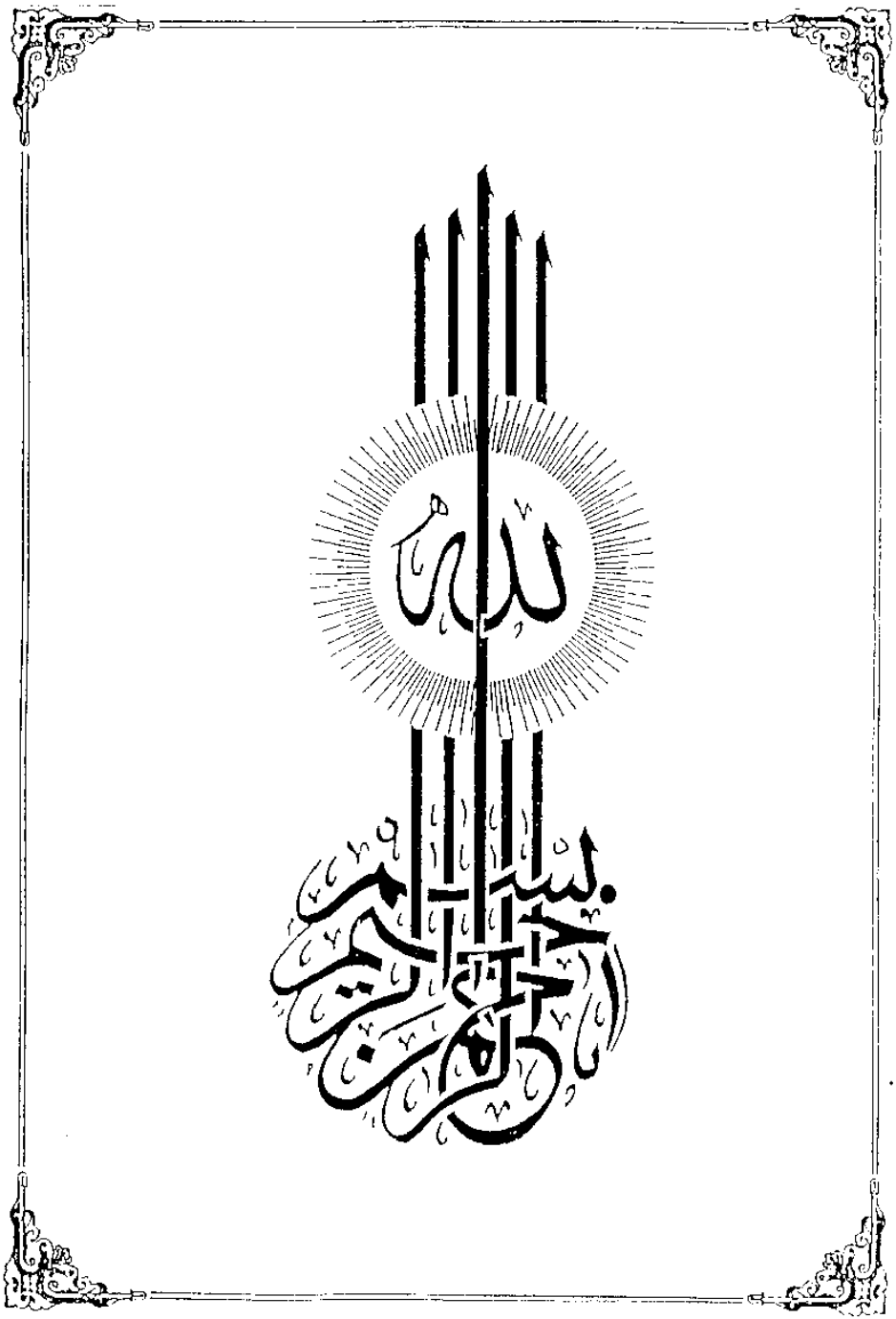
I Wish to express my lasting and sincere gratitude to Prof. Dr: Samir Hanna, professor of the clinical pathology, Ain Shams University for his continuous encouragement and kind help.

I wish to express my lasting and sincere gratitude to prof. Dr: Ali Rashed, Head of educational affairs, Medical Military Academy for his continuous encouragement and kind help.

I also like to express my sincere thanks and appreciation to Dr: Mona Rafik, lecturer of clinical pathology, Ain Shams University for her valuable assistance, sincere guidance and supervision through the work.

Finally I like to thank all members of clinical pathology department, Ain Shams University for their supportive help and encouragement.

* * * * * * * * * * * *



LIST
OF
A B B R E V I A T I O N

AIDS:	Acquired Immuno Deficiency Syndrome.
ARC:	AIDS - Related Complex.
ATL:	Adult T-cell Leukaemia / Lymphoma.
BLV:	Bovine Leukaemia Virus.
ELISA:	Enzyme - Linked Immunosorbance Assay.
gag:	Group specific antigen.
gp:	Glycoprotein.
HTLV:	Human T-Lymphotropic Virus.
IDAV:	Immuno Deficiency - Associated Virus.
IFA:	Immunofluorescent Assay.
IL1:	Interleukin 1.
IL2:	Interleukin 2.
LAV:	Lymphadenopathy - Associated Virus.
LTR:	Long Terminal Repeat.
NK:	Natural Killer.
TAT:	Trans-Acting Transcriptional regulation.

* * * * * * * * * *

TABLE

OF

C O N T E N T S

* * * * * * * * * *

INTRODUCTION AND AIM OF WORK

Acquired Immune Deficiency Syndrome is a devastating disease consisting of impaired immune functions. Epidemiological evidence suggests that this syndrome is caused by an infectious agent transmitted by blood parentral means or sexual contact (Francis et al., 1983).

The etiologic agent of the acquired immune deficiency syndrome is a newly recognized retrovirus called Human T-lymphotropic virus (HTLV-III) (Gallo et al., 1984).

Serum antibodies to this virus have been detected in the majority of patients (68%-100%) with AIDS and AIDS related complex (ARC) or related conditions (Safai et al., 1984). Seropositivity rates in groups at increased risk for AIDS are variable e.g. healthy homosexual men, 22% - 65% (Weiss et al., 1985) and intravenous drug abusers 87% (Spira et al., 1984).

The AIDS virus has been isolated from blood of 85% or more of seropositive high risk individuals with AIDS or blood donors implicated in the transmission of AIDS through transfusion (Carlson et al., 1985). In contrast to the high risk groups virus or antibody has been detected in less than 1% of persons at risk for AIDS (Weiss et al., 1985).

Therefore serological testing for antibodies to the AIDS retrovirus should be an effective means to detect most persons that have been exposed to the AIDS virus and who are potential carriers of this infectious agent (Carlson et al., 1985).

Thus the aim of this study was to screen a population at high risk (homosexual male prisoners) for the presence of the HTLV-III antibody to detect previous exposure to the virus in our community.

* * * * * * * * * *

HISTORICAL REVIEW

In 1872, the Hungarian dermatologist Moritz (Kohn) Kaposi described multiple idiopathic haemorrhagic sarcoma, a rare multifocal sarcoma that generally begins as small violaceous papules and nodules on the lower extremeties of elderly men. The disease did not recieve widespread attention until the 1960's when it was recognized that large numbers of cases of Kaposi's sarcoma occurred in equatorial Africa. The African cases were extensively studied by Templeron and Huh (1973). In addition to the classical nodular presentation, three additional clinical presentations were recognized, an exophric or florid form, an infiltrative form and a lymphadenopathic form.

In the 1970's it was realised that Kaposi's sarcoma was seen as an opportunistic malignancy in individuals who were iatrogenically immunosuppressed. Two reports were presented as confirmation that immunosuppression was pivotal to the appearance of the disease. One of these cases was temporal arteritis and the other was asthma, both of which were treated with the prednison and Kaposi's sarcoma developed after the patient was immunosuppressed. In both instances, the corticosteroids were discontinued and the Kaposi's sarcoma totally regressed as the patients' immune systems recovered. (Marcus, 1984).

In the summer of 1981, the Centers of Disease Control (C.D.C) reported cases of Kaposi's sarcoma from New York and a variety of opportunistic infections from Southern California. Both these highly unusual outbreaks were combined as a single report because they shared the epidemiologic features of occurring in young homosexual men who had been sexually promescious. Thus the first appearance of what has come to be called the acquired immune deficiency syndrome (AIDS) occurred. This outbreak appears to be the first documented epidemic of community-acquired immune dysfunction.

In retrospect, it would appear that there were two or three cases in 1970, seven or eight cases in 1979, and then an exponential rise in the number of cases since that time (Marcus, 1984). By November of 1983, over 2753 cases had been reported in the United States (Marcus, 1984). Half of these cases had presented with pneumocystis pneumonia carinii, pneumonia without Kaposi's sarcoma, and only 25% of cases had presented with Kaposi's sarcoma without pneumocystis pneumonia.

An increasing number of foreign countries began to report cases of AIDS. As of November, 1983, 50 cases had been reported from Canada, with an epidemic pattern almost identical to that seen in the United States. The European cases reported as of October, 1983, showed that twenty two percent of the 268 European cases were individual born in Africa and 37% were women. This was particularly significant since in the United States and Canada and in many Europeans with AIDS only about 5% of the cases had occurred in women.

In Haiti and Zaire intractable diarrhea and progressive tuberculosis appear to be the two most common manifestations of AIDS followed by oesophageal candidiasis and toxoplasmosis, (Marcus, 1984). Pneumocystis pneumonia is seen less frequently and Kaposi's sarcoma is rare. This is clearly a different pattern of disease than that reported in the United States and Europe, but it may represent the same syndrome in a developing nation, (Marcus, 1984).

Between June, 1981 and July 1985 11,871, cases of which 11,724 adult and 147 pediatric cases of acquired immune deficiency syndrome (AIDS) were reported to the Center for Disease Control (CDC), (Curran, 1985). Of these patients 5, 917 (50 %) have died. Of the adult cases, 69,9% were under 40 years of age, 10, 952 (93.4 %) were men, 73.2 % were identified as homosexuals or bisexuals in orientation. Cases have been reported from 46 states and the district of Colombia with nearly 36.1% from New York State (Curran, 1985).

Reported incidence of the acquired immune deficiency has steadily increased since June, 1981. This increase reflects increases in cases among all population at increased risk and all geographic areas (Curran, 1985). Another 10,000 cases are expected to be diagnosed between April 1985 and April 1986, (Nevalainen., 1985). It is estimated that perhaps as many as one million people have been infected with the AIDS virus and that perhaps 1% or 2% of these people annually may comedown with clinical AIDS in the years ahead (Nevalainen, 1985).

The disease appeared to be transmitted by close intimate contact (heterosexual and homosexual) and is passed by exchange of semen, saliva and mucus membrane contact. AIDS is also transmitted parentrally, most frequently in intravenous drug users, and via the transfusion of blood and blood products. Vertical transmission has also been documented, both in utero and perenatally (Nevalainen, 1985). In general the infection follows patterns similar to these seen for hepatitis B (Niejadlik et al., 1985).

Gallo proposed that AIDS was likely to be caused by a human T-lymphotropic retrovirus in February, 1982 at the Cold Spring Harber Conference on AIDS. Experiments were initiated to test this hypothesis in July, 1982. Barre - Sinoussi et al., (1983) reported detection of an arbovirus in T cells of one lymphadeno-pathy patient utilizing the same treatment protocol developed for HTLV-I with minor modifications. They were also able to temporarily transmit this virus to normal T cells and recognized it to be a human T lymphotropic retrovirus. This virus was first called LAV (lymphadenopathy associated virus), later IDVA (Immunodificiency associated virus) and then LAV, by this group. Their early work showed that only 20% to 30% of sera from AIDS patients contained LAV specific antibodies. Thus when Popovic et al., (1984) obtained 90% or greater positive antibody results to HTLV-III with AIDS sera, it was not immediately certain that the virus was the same (Gallo, 1985). Now it is clear that LAV and multiple isolates of HTLV-III are variants of the same virus (Gallo, 1985).

Gallo et al., (1985) originally reported 48 isolates of HTLV-III from T cells of AIDS, pre-AIDS and risk groups. They have now over 100 isolates of HTLV-III. By making repeated attempts and by the use of hydroxycorticosteroids, they have increased the incidence of virus isolation to more than 80% in pre-AIDS and have achieved an almost equally high incidence in AIDS. Culture of peripheral blood T cells from people belonging to a known risk group (i.e. drug users, Haitians, prostitutes and promiscuous homosexuals) yielded virus in 30% where culturing these cells from over 150 normal healthy heterosexuals did not yield detectable virus in any. Originally these isolates of HTLV-III were obtained from blood, bone marrow, lymph nodes and spleen. More recently the virus has been isolated from plasma as infectious extracellular particles Gallo et al., (1985). These findings are consistent with the association of AIDS with whole blood or factor VIII transfusions.

Considerable epidemiological evidence suggests that AIDS is linked to sexual practice. However, the virus had not been identified in semen until recently (Zagory et al., 1984). Somewhat unexpectedly, HTLV III was isolated from saliva of pre-AIDS patients and from several healthy homosexuals (Groopman, 1984). Epidemiological studies indicate that HTLV-III is not

transmitted by saliva (e.g. Sneeze, Cough etc.) but there are no data to exclude heavy salivary exchange as a mode of transmission.

It has now been established that the primary cause of AIDS is an infection with a variant of HTLV-III (Krohn et al., 1985). Antibodies to HTLV-III are frequently found in cases with AIDS, ARC or LAS but also in asymptomtic homosexual men (Krohn et al., 1985).

* * * * * * * * * *

DEFINITION OF: AIDS AND RELATED CONDITIONS

I- Acquired Immune Deficiency Syndrome

The case definition of AIDS, as described by the Center For Disease Control has the following features. (Table 1).

1. Kaposi's sarcoma proven by biopsy and or life threatening opportunistic infection proven by biopsy or culture.

2. Occuring in a previously healthy person under the age of 60.

3. With no conditions known to cause immunosuppression such as congenital immunodeficiency or therapy with immunosuppressive agents.

According to CDC definition pediatric AIDS occurs in children below the age of 13. In particular congenital infections and congenital immunodeficiency conditions must be excluded. Pediatric AIDS is primarily a disease of infants and toddlers with 19% of the cases occuring in children under 3 years of age. The majority of these infants are born to parents in a high risk group or have a parent with AIDS. The next most common setting for

pediatric cases is transfusion associated AIDS. Immunologic testing is not required for inclusion of persons meeting the case definition, (Jaffe et al., 1983).

Definitions of AIDS and Related Conditions

AIDS—SURVEILLANCE DEFINITION OF THE CENTERS FOR DISEASE CONTROL

The occurrence of a disease that is at least moderately predictive of a defect in cell-mediated immunity, occurring in a person with no known cause for diminished resistance to that disease. These diseases include:

- Kaposi's sarcoma (in patients <60 years of age)
- Primary lymphoma of the central nervous system
- *Pneumocystis carinii* pneumonia
- Unusually extensive mucocutaneous herpes simplex of >5 weeks' duration
- *Cryptosporidium* enterocolitis of >4 weeks' duration
- Esophagitis due to *Candida albicans*, cytomegalovirus, or herpes simplex virus
- Progressive multifocal leukoencephalopathy
- Pneumonia, meningitis, or encephalitis due to one or more of the following: *Aspergillus, C. albicans, Cryptococcus neoformans*, cytomegalovirus, *Nocardia, Strongyloides, Toxoplasma gondii, Zygomycosis*, or atypical *Mycobacterium* species (excluding tuberculosis and lepra).

PEDIATRIC AIDS—PROVISIONAL SURVEILLANCE DEFINITION OF THE CENTERS FOR DISEASE CONTROL

Same as AIDS in adults, with the following provisions:

A. Congenital infections that must be excluded are:
   1. *T. gondii* in patients <1 month of age
   2. Herpes simplex virus in patients <1 month of age
   3. Cytomegalovirus in patients <6 months of age

B. Specific conditions that must be excluded in a child are:
   1. Primary immunodeficiency diseases: severe combined immunodeficiency, DiGeorge syndrome, Wiskott–Aldrich syndrome, ataxia-telangiectasia, graft-versus-host disease, neutropenia, neutrophil function abnormality, agammaglobulinemia, or hypogammaglobulinemia with raised IgM
   2. Secondary immunodeficiency associated with immunosuppressive therapy, lymphoreticular malignancy or starvation

Goedert and Blattner, 1985.

II- Lesser AIDS:

Lesser AIDS, a term that is not used widely, is intended to be an adjunct to the Centers for Disease Control surveillence definition of AIDS (Goedert et al., 1984). Lesser AIDS includes a specific group of non-life