HIV - ANTIBODY AMONG TUBERCULOUS PATIENTS IN ZAMBIA

BY

DR SHUWANGA SIMASIKU BSc (HB), MBChB - UNZA

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DECLARATION

I hereby declare that the work presented in this study for the degree of Master of Medicine (M.Med) SURGERY, has not been presented either wholly or in part for any other degree and is not being currently submitted for any other degree.

STATEMENT

I hereby certify that this study is entirely the result of my individual effort. The various sources to which I am indebted have been acknowledged in the paper and in the bibliography.

DEDICATION

TO MY WIFE CATHY AND CHILDREN, MATOMOLA AND LUNGOWE.

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ABSTRACT

Sera from 72 tuberculosis patients obtained from U.T.H. (Urban - 40 patients) and Katete (Rural - 32 patients) and 144 controls matched for age and sex were analysed for anti-bodies to HIV. The testing was by a specific competitive enzyme linked immunosorbent essay (ELISA) technique - the WELLCOMYME-HTLV-II test.

The positive sera were not subjected to further testing by western blot technique. Seropositivity for HIV among tuberculosis patients was 43% as compared to 15% seropositivity among controls (P Value - 0.0000001 and ODD ratio of 3). The seropositivity to HIV among the urban patients (57.5% of 40 patients) is twice as much as the seropositivity among the rural patients (25% of 32 patients). The seropositivity is also higher among the urban controls (22.5%) than among the rural counterparts (6.2%). 46 female and 26 males were seen. Of the 46 females, 22 were seropositive whereas 9 of the 26 males were seropositive. There was no significant increase of seropositivity with increasing age. However, the peak of seropositivity occurred between the ages of 25 and 35 years of age. There was also no significant difference in weight gains between seropositive and the seronegative TB patients on the same standard anti-tuberculosis chemotherapy. Seropositivity was highest among the extrapulmonary TB patients: 88.9% for TB lymphadenitis, 71.4% for pleural effusion and 50% for TB peritonitis, (whereas PTB had only 31.5% seropositivity). This data shows that there is a high correlation between HIV seropositivity and tuberculosis.

CHAPTER 1

INTRODUCTION

The Aquired Immunodeficiency Syndrome (AIDS) was first reported in the USA in May, 1981 (1,2). Cases of AIDS have been reported in 74 countries (WHO, Paris 1986) and it is estimated that over a million people are infected by human T-Lymphotropic Virus, type III; recently called Human Immunodeficiency Virus (HIV) (3,4). More than 25,000 cases in the USA, nearly 3,000 cases in other countries of America, more than 3,000 cases in Europe and several thousands of cases suspected and many more unrecognised in Africa. Because of its rapid spread, high mortality rate and lack of treatment, AIDS is the major health problem of the decade (5). In the USA and Europe, risk groups have been identified; Homosexuals which account for over 70% of cases (5), Haemophiliacs, Haitian Immigrants, intravenous drug abusers, infants born to infected mothers and partners of AIDS patients. Since its discovery, AIDS epidemics have been reported in the USA, Europe and Africa (6).

In Africa, the disease became known in 1982/83 as many affluent Africans in France, Belgium and the UK, were being diagnosed as having AIDS (7,8,9,10). In contrast to the AIDS in the USA and Europe, African AIDS is reported to be common among heterosexuals (11,12,13). Since then, more and more cases have been reported in Rwanda (14), 600 cases per million population in Kigali, and in Zaire, 170 cases per one million population in Kinshasa. As of March, 1986, 177 cases of AIDS have been reported among Africans residing in ten European countries (12).

In Zambia, the problem of AIDS emerged when cases of Kaposi Sarcoma (KS) presented atypically with lesions in unusual sites from 1982 onwards (15,16). Ninety percent of cases of atypical KS were seropositive for HIV antibodies against 2% in the control group (16). Furthermore, a Zambian nurse who died in the UK was reported as having AIDS (7).

The causative organism has been identified and named Human T cell lymphotropic leukaemia virus type III (HTLV-III) (Gallow et al 1984), now known as Human Immunodeficiency Virus (HIV), or Lymphadenopathy Associated Virus (LAV) (Monthagniers Group 1983 - Paris). Infected with this human retrovirus HIV/LAV can be detected by testing the sera for antibody against the virus (17,18,19). Pulmonary complications resulting from opportunistic infections are common in AIDS and they are the major cause of death (20,21,22). In the West, pneumocystic carinii pneumonia (PCP) is the commonest of all opportunistic infections including Cytomegalovirus (cmv) Cryptococcosis, Herpes Zoster, Oral candidiasis, atypical mycobacteriosis (non-tuberculosis) (23,24) and Mycobacteria tuberculosis homini have been reported (20,21,22,23,25,26). Mycobacteria tuberculosis may prove pathogenic to the seropositive patient and that in the absence of a normal host response the disease produced may be more severe and present in an atypical way (27). The histopathology is atypical because of the absence of typical granulomatous lesion: the classical tubercles characterised by central caseation, surrounded by a pallisade of histiocytes and lymphocytes and Langerhan's giant cells (21,26).

There are two important and obvious interrelationships of Mycobacteria tuberculosis and HIV infection:

(a) That compromised immunity due to HIV infection may favour activation of pre-existing latent mycobacteria tuberculosis since other immunosuppressive disorders are associated with an increased risk of developing clinically apparent tuberculosis.

(b) That an initially seronegative person has tuberculosis and due to the resulting immunosuppression acquires HIV infection as an opportunistic infection.

Hypothesis A - can be tested by following up all positive patients for HIV but without tuberculosis at the time they are found seropositive and therefore, see how many would acquire tuberculosis in the long term. Hypothesis B, can be tested in the long term by repeating HIV antibody tests in seronegative tuberculosis patients and their controls after a

given interval, eg. 6 months. The present study however, does not intend to answer either of the above hypothesis.

AIMS AND OBJECTIVES

This study has the following objectives:-

(a) To determine the prevalence of HIV infection (seropositivity in tuberculosis).

(b) 1. To determine the effect of HIV infection on the response to standard anti-tuberculosis chemotherapy.
2. To determine the incidence of Stevens-Johnson Syndrome during Chemotherapy.

(c) To determine the clinical type of tuberculosis (pulmonary or extra-pulmonary), with the highest incidence of HIV infection (seropositivity).

This study will be able to tell us the magnitude of HIV infection in our tuberculosis patients so that appropriate strategies in the medical care of tuberculosis are formulated. It will also be able to tell us whether or not there is correlation between HIV infection and tuberculosis.

DEFINITIONS OF TERMS

For the purpose of this study, the following definitions will be used:-

Patient - The term "patient" will be used to refer to a tuberculosis patient. Tuberculous patient will be used to refer to a person who in addition to having clinical features of tuberculosis, will also have a positive sputum for alcohol and acid fast bacilli either by Ziehl-Neelsen

staining or by culture and sensitivity, or positive histopathological report.

Tuberculous Disease - will be used to refer to a person who is infected by tubercle bacilli (m.Tuberculosis) and also shows signs and symptoms of the infection.

Tuberculous Infection - will be used to refer to infection with mycobacteria tuberculosis as evidenced by a positive Mantoux or Heaf Tests but without signs and symptoms of the disease.

Tuberculosis (TB) - will be used to refer to a disease due to a mycobacteria tuberculosis.

Pulmonary Tuberculosis (PTB) - will mean tuberculosis affecting the lungs.

Extrapulmonary Tuberculosis - will mean tuberculosis in other sites apart from the lungs, eg. TB lymphadenitis, TB peritonitis and TB arthritis.

Control - will mean a person ill or healthy who does not have tuberculosis, may be seronegative or seropositive to HIV infection but have no AIDS.

AIDS - will mean Acquired Immunodeficiency Syndrome.

HTLV - will mean Human T-cell Lymphotropic Syndrome.

HTLV I - will mean Human T-cell lymphotropic Virus type I

II - will mean Human T-cell lymphotropic Virus type II

III - will mean Human T-cell lymphotropic Virus type III.

HIV - will mean Human Immunodeficiency Virus Synonymous with HTLV-III.

HIV - infection - will mean infection due to HIV detected by the presence of antibodies against HIV - but do not have AIDS, as laid down by WHO (Table 1).

ELISA - will mean enzyme linked Immunosorbent assay.

LAV - Lymphadenopathy Associated Virus.

RATIONALE OF THE STUDY

The epidemic of AIDS and HIV infection was heralded in Zambia by Bayley A C (1984) (15,16). Subsequent preliminary reports of HIV seropositivity in patients attending the sexually transmitted disease (STD) Clinic (UTH 30% seropositivity) showed a high incidence. Tedder A C, in Lusaka, August, 1985, reported a 15% seropositivity in the general public. Such results prompted the Zambian Government through the Ministry of Health to adopt the AIDS Task Force and the National Surveillance Team whose jobs were to institute and approve research programmes and to inform and advise the Government on the nature of AIDS and HIV infection.

Tuberculosis is a national health problem in Zambia. As a result, every District or Provincial Hospital has a TB Ward. In UTH alone, in the year ending December, 1985, there were 1,743 cases of TB against a total admission of 96,068. Although TB IS REPORTED TO BE ON THE DECLINE IN THE USA, as shown by the figures for 1977 - 35,145 cases (13.9 per 100,000 population) and 1984 - 22,255 cases (9.4 per 100,000 population), a drop of 3.5 per 100,000, the incidence of tuberculosis has been noted to be on the increase in New York City, California, Florida and Texas, which are some of the areas where the largest number of AIDS cases have been reported to date (29). Similar observations have been reported among Haitians (23). Out of 45 Haitians with AIDS, 27 cases had TB. Twenty-two (22) of the 27 cases had tuberculosis before the onset of AIDS (23). Furthermore data from New York City indicate that increased tuberculosis morbidity is

occurring in areas of the city with the highest number of AIDS cases. When the New York City tuberculosis and AIDS registers were matched, they revealed that a number of AIDS patients had histories of tuberculosis (29). It is against this background that a study like this one was undertaken to examine the relationship of HIV infection and tuberculosis in Zambia.

CHAPTER 2

REVIEW OF LITERATURE

"The human race must have a common strategy against AIDS otherwise the disease will conquer man. We should avoid wasting money and energy quarrelling because we shall not be aiding anyone but AIDS", said His Excellency President K D Kaunda (30).

The Acquired Immune Deficiency Syndrome (AIDS) is defined clinically by the Centre for Disease Control Surveillance as a disease at least moderately predictive of a defect in cell mediated immunity occurring in a person with no known cause of diminished resistance to that disease (1,2). The disease is characterised by opportunistic infection and malignant disease in patients without a known cause of immunodeficiency. AIDS has a high mortality rate (1,20).

Between 1st June, 1981 and September, 1983, there were 593 cases of AIDS and of these, 243 (41%) were dead. With present lack of curative therapy or vaccine this disease ranks as the most serious epidemic of the century (12). AIDS has also been described as a tragedy for mankind. Within approximately 5 years the AIDS epidemic has spread to all parts of the world. By the 20th October, 1986 (WHO,21), a total of 33,217 AIDS cases had been reported to WHO from 101 countries representing all continents. Of these, 23,217 cases 86% are in the USA whereas Europe 3,245 cases, Asia 55 cases, Oceania (Australia and New Zealand) 317 cases and Africa, 1,008 cases.

Right from the beginning, AIDS was described among homosexuals who account for 73% of all cases in the USA (1,20). The same group was found at risk even in Europe (12). Since it is common in homosexuals and bisexual men, the male to female ratio in USA and Europe is 16:1 (6,12). Other risk groups identified in the USA and Europe are Haemophiliacs, intravenous drug abusers, children born to mothers with AIDS or HIV infections. Homosexuals

having persistent generalised lymphadenopathy (PGL) have a higher incidence of seropositivity risk than homosexuals without it (19).

Shortly after the recognition of AIDS in the United States, cases of the disease were identified among Africans resident in Europe (8,9,32). Immunologically, these cases were identical to AIDS cases in the United States with a marked depression of T4 lymphocytes (t-helper cells) and cell mediated Immunodepression. Clinically, the African AIDS cases resembled Haitian AIDS cases with prominent gastrointestinal symptoms and opportunistic infections such as mycobacterial infection, cryptococcosis toxoplasmosis and oesophageal candidiasis (8,9,23). The earlier cases described in Europe originated from Central Africa - Zaire (8,32), Rwanda (8,9), Zambia (7) and Mali (10).

In contrast to the European cases, African cases have a male to female ratio of 1:1 and 90% of the latter cases have no identifiable risk factors. In 1983, from studies in Zaire (13) and Rwanda (14), there were 38 patients with AIDS - related disease in Kinshasa and 26 cases in Kigali. Of the 26 cases, 43% of the females were identified as prostitutes (14). It may be hypothesised that the increases in the incidence of certain diseases in Africa could have been due to the increase/or presence of AIDS (12). Epidemic increases in the chronic life threatening enteropathic illness noted in the late 1970s in Kinshasa (13) and in early 1980s in Uganda (33) and Tanzania where this disease is known as Slim Disease. In Rwanda, a marked increase in Oesophageal candidiasis was first noted in 1983 in a hospital where approximately 300 oesophagoscopies had been performed annually since 1979 (13). In Kinshasa again the annual number of Kaposi Sarcoma diagnosed in a large hospital tripled from 1970 to 1984 and the number of aggressive Kaposi Sarcoma increased eight times in 1981 (13). In Zambia (15,16) and Uganda (16), there was a reported marked increase in disseminated Kaposi Sarcoma starting in 1982 and 1983. Finally, careful surveillance of cryptococcal meningitis in Kinshasa showed a sevenfold increase in 1978 - 1984, compared with the 1953 - 1977 figures (10). These studies suggested that while isolated cases of AIDS may have occurred in Africa earlier, it was probably rare until late 1970s and early

1980s, that a pattern similar to that of the United States and Haiti (12) developed.

AETIOLOGY

For approximately 3 years, the aetiological agents for AIDS remained unknown. Diagnosis was based on Immunodeficiency characterised by lymphopenia and reversed T-helper to T8 suppressor cell ratio and by the presence of opportunistic infection such as pneumocystic carinii pneumonia and Malignancy - Kaposi Sarcoma (KS) (1,2). In 1983 Montagnier's group in Pasteur Institute, Paris, described the isolation of T-lymphotropic virus from a patient at risk for Acquired Immunodeficiency Syndrome (AIDS) and called it the Lymphadenopathy Associated Virus (LAV) and AIDS related virus (ARV) (34). Later, Gallo's group from the National Cancer Institute, Bethesda, USA described the isolation of cytopathic retrovirus from patients with AIDS and at risk for AIDS - Popovic Metal which they called Human T-cell Lymphotropic Virus type III (HTLV-III). Further research showed that after all these two types of viruses were similar/identical. This virus is known to belong to the retrovirus family which has been known for more than 50 years (12). There are 3 types of human retroviruses. HTLV-I first isolated in Japanese Leukaemic patient and now described in Central Africa, the Caribbeans and the USA, causes Leukaemia. HTLV-II isolated from a patient with HAIRY Leukaemia is not linked with any disease. HTLV-III now called HIV is the causative agent for AIDS. These retrovirus have many features in common.

1. They are exogenous viruses isolated from mature T-cells especially T4 cells.

2. They infect mature T-cells in vitro although all cells can serve as targets for infection under certain instances.

3. They produce reverse transcriptase with similar biochemical features.

4. They possess some cross-reacting antigens.

5. They have a major core protein of similar size.

6. They exhibit some homology in nucleotide sequence.

7. They have a pX sequency at 31 end of the genome.

8. Upon in vitro infection of the T-cell, they induce formation of multinucleated giant cells. Whereas HTLV-I and II are stable viruses, HTLV-III has a high replicating rate and shows variability in its env gene region (37). Once infected, a person may well stay infected for life.

Following the isolation of HIV/LAV from AIDS patients in the USA and Europe, several studies were done on African patients with AIDS. For example McCornick Jetal (6) isolated HIV from 27 (77%) of 35 African patients with AIDS and from 5 of 9 patients with AIDS related complex. Further evidence of HIV/LAV as the aetiological agent in Africans is given by the isolation of human T-lymphotropic retrovirus (LAV) from Zairean married couple, one with AIDS and the other with the Prodrome (33). The situation in Africa has been complicated by the discovery of other retroviruses in West Africa from AIDS patients and monkeys (6,12,38). The Myron Essex's group isolated a retrovirus from people without AIDS particularly prostitutes in Senegal which was referred to as HTLV-IV (39). This retrovirus appears to cross-react serologically with HIV and more strongly, with STLV-III AGM, a recently described isolate from healthy wild caught African Green Monkeys. The other viral isolate by Luc Montagniers group, referred to as LAV-2 was recovered from AIDS patients in Guinea Bissau and Cape Verde Islands (40). The same retrovirus was isolated from AIDS patients in neighbouring countries and renamed it HIV-2 (41). LAV-2 cross-react strongly with STLV-III MAC, a primate retrovirus isolated from captured macaques. In contrast to HIV neither HTLV-IV nor LAV-2 induced antibody to the glycoprotein gene-gP41, commonly seen in HIV infected individuals (12). Unfortunately, there has been no direct comparison of HIV-2 and HTLV-IV because of lack of cooperation between the French and USA Researchers (27). Up to December, 1986, no genome comparisons of HTLV-IV, LAV-2 and HIV had been done.

ANTIBODY DETECTION

With the isolation of HIV as the aetiological agent of AIDS, a clearer understanding of its natural history emerged (12). Since the isolation of human-lymphotropic virus type III (HTLV-III/Lymphadenopathy Associated Virus LAV) from patients with AIDS, antibodies against these viruses have been detected in AIDS patients (18,42). Antibodies to HIV have been found in more than 90% of patients with AIDS and in 80 to 100% of people with AIDS related condition such as unexplained persistent generalised lymphadenopathy (PGL) (43). Seropidemiological studies and blood bank screening programmes mostly use the enzyme linked immunosorbent assay (ELISA) because it is rapid and economical. It has proved to be sensitive and specific when dealing with sera from members of different risk groups in Europe and the United States (Weiss S H et al), but ELISA tests may need to be used with caution on sera from Africa (44), and perhaps other tropical areas. The new commercially available ELISA is reported to be specific for HIV antibodies even in Malarial areas of Africa (12). For example, Francis H, et al, in a study of 400 AIDS patients and 100 healthy controls in Zaire reported a 99% and 98% sensitivity and specificity respectively.

Ninety-eight percent of the sera, repeatedly positive by ELISA were also found by Western Blot to have a protein band characteristic of HIV Infection. In Zambia, a highly specific test WELLCOZYME test using competitive immunoassay is available in the University Teaching Hospital and is currently being used for screening blood donors (45). In a recent study in Lusaka, Zambia, of 1078 subjects, 17.5% were seropositive. All the positive and negative results with the competitive ELISA test were confirmed by Western Blot (11). Another ELISA test available in NDOLA-Tropical Disease Research Centre uses an antigen ENV-80 DHER: a conserved part of the membrane glycoprotein gp 41 of HIV derived by recombinant technology.

The Western Blot technique is considered to be the most specific confirmatory assay (46). The test uses electrophoretic separation of virus proteins (p) and glycoprotein (GP) to give a profile of bands

characteristic of HIV when antibody positive sera are applied. The bands specifically recognised in relation to HIV are P15-18, P25-25, GP41-55 and P64 which represent both viral core antigent and envelope antigens.

MODES OF TRANSMISSION

HIV has been isolated from the blood of lymph node and the virus has been recovered from over 90% of patients with early AIDS (46). It has been isolated from other body fluids and tissue eg. saliva (47), semen and blood (48), cerebrospinal fluid and brain tissue (Levy), (49) bone marrow cells, cell free plasma and tears (50). In theory exposure to any of these body fluids if contaminated with the virus represents a risk. In North America and Europe, transmission of HIV infection had been documented to occur through one or more of the four modes (51,52): a) Sexual contact b) exposure to contaminated needles c) administration of infected blood or blood products and d) the passage of the virus from infected mothers to their newborns. In contrast to North America and European AIDS patients, African AIDS patients rarely report a history of homosexual activity or intravenous drug abuse (11,13,45,53). Although it may be difficult to ascertain homosexual activity and drug abuse because of cultural differences, evidence shows that these two risk factors do not play a major role in HIV transmission in Africa (12). Available data suggest that heterosexual activity (11,13,53), blood transfusions (3), maternofetal transmission from mother to infant (45) and probably exposure to unsterilized needles account for the spread of HIV infection and AIDS in Africa. Of these modes of transmission, heterosexual activity and exposure to unsterilized needles and blood transfusion may seem to be the main routes of exposure among tuberculosis patients with AIDS or HIV infection (11,12). In the USA the rising incidence of tuberculosis in cities with the highest rate of AIDS cases suggest that homosexual activity is the main mode of exposure (30). In Africa, Mann J M et al noted among adult patients with tuberculosis, that HIV seropositives reported significantly more injections than seronegatives during the 5 year period prior to hospitalisation. The use of blood contaminated needles has been suggested (34) as a means of transmitting HIV amongst tuberculosis, especially in

Africa where the economies may not permit frequent supply of disposable needles (11,12). It is also reported that most patients often express strong preference for parenteral rather than oral therapy. In Kinshasa, Zaire, (Ngally B) reported that 84% of 50 mothers expressed the belief that parenteral medication is more effective than oral medication.

Several lines of evidence support the concept that HIV infection is transmitted heterosexually in Africa (8,9,11,13,14-54, 53,55). In addition to the 1:1 male to female ratio (13) among AIDS cases, and the young age and single marital status of female cases, case controlled studies have shown that AIDS patients have a significantly higher number of heterosexual partners than controls (11,13,45,53), that male patients have had sex significantly more often with female prostitutes (53), and that the risk of seropositivity increases significantly with the number of different sexual partners per year and with a history of sexually transmitted disease (13,14,27). In Rwanda and Kenya, the seropositivity to HIV antibody among prostitutes is between 27% and 88% (53). The risk factors associated with HIV infection in heterosexuals include number of sexual partners (11,13,14,45), sex with prostitutes (53), being a prostitute and being a sexual partner of an infected partner (33,45,55).

AIDS AND IMMUNITY

The Acquired Immunodeficiency Syndrome (AIDS) is a novel, epidemic form of the immunodeficiency. A number of immunologic abnormalities have been described (see Table 2). HIV is known to have a positive tropism for activated T4 Lymphocytes. The complete spectrum of immunologic dysfunction in the syndrome is reported to be explained by the preferential infection of T4 helper/inducer lymphocytes and the resultant functional changes in immunity due to specific lack of function of these vitally important cells (58). Despite all this knowledge the pathogenesis of AIDS is still not fully elucidated (58). Many of these immunologic abnormalities seen in AIDS may be secondary to the host response, although some could be direct effects of HIV infection. Although HIV is known to have certain effects that are undoubtedly important, such as lysis of T-helper cells, these

known direct effects may not fully account for the immunodeficiency state (59). The lack of knowledge is worsened by the fact that the majority of people who are found to be seropositive to HIV are asymptomatic. The viral interaction with the immune system in these people is not completely understood. However, several cross sectional studies have found a correlation between seropositivity and a lower phytohaemagglutinin response, higher Ig 'G' concentration, raised concentration of immune complexes and an inversion of the T-helper to T-suppressor ratio. More recently Melbye M and Biggar R J (62) reported that the changes in the T-helper to suppressor ratio is associated with the duration of seropositivity in longitudinal follow-up of homosexual men. They also reported that the inverted ratio is due initially to both a rise in T suppressor and a decline in T-helper cells, which makes the ratio the single best predictor of seropositivity. It is reported that people who have been seropositive for a long time, may suddenly have an unexplained fall in the T-helpers cells and total cells. These individuals are said to have a high risk of developing AIDS (62).

Histologically, the Lymph nodes of the patients are reported to show follicular hyperplasia with or without parafollicular hyperplasia, some show follicular involution or a mixed pattern (63). Immunohistologic studies have demonstrated infiltration of germinal centres by T8 cells, disruption of the germinal centre follicular dendritic reticulum - cell structure, depletion of T4 cell with a predominance of T8 cells in T-cell areas and plasma infiltration (64).

TUBERCULOSIS

"Tuberculosis continues to be one of the most prevalent and serious diseases in the world. The varied and sometimes profound immune responses induced be Mycobacterium tuberculosis are not only responsible for immunity but can cause considerable damage and metastasis....." Bulletin WHO. Tuberculosis the WHITE PLAGUE of centuries past has become a condition that is today not only treatable and curable, but preventable as well. Tuberculosis has been with mankind for centuries and the Hypocrites called

pulmonary tuberculosis PHTHISI. For many years, the agent remained unknown until in 1882 when Robert Koch isolated the organism (bacilli), cultured it, inoculated into animals to produce the disease, and was able to isolate the bacilli from these animals. Hence the Koch phenomena became known.

Sir William Osler observed that tuberculosis was a social disease, half a century ago (66). In 1982, the WHO estimated that about 20 million people are suffering from active tuberculosis in the world and that 3 million people die annually due to tuberculosis (65). Whereas in the developed countries tuberculosis no longer poses a major health hazard, it is still serious in developing countries, taking a heavy toll and causing untold physical, social and economic suffering (66). The prevalence of tuberculosis is on the decline in the USA. (Tables 3,4) (20,30,67). The prevalence of tuberculosis among Haitians entering Southern Florida, is high, 650 per 100,000 population compared with prevalence in the United States population as a whole of 11 cases per 100,000 population (23).

In Zambia, tuberculosis is a major problem. The incidence of tuberculosis is still high. The total notification for the year 1985 was 8,347,of whom 5,560 cases had pulmonary tuberculosis (Ministry of Health - Zambia). The incidence of pulmonary tuberculosis in the University Teaching Hospital, Lusaka, show an increase since 1980 (Table 5, Hospital Records). It is reported that Zambia contributes 6% of tuberculosis notification to WHO in the whole of Africa and yet her population forms only 1% of that of Africa (Ministry of Health).

CAUSATIVE AGENT

The tubercle bacillus has been known since 1882 when it was first described by Koch. Mycobacteria tuberculosis possesses the capability of taking up water soluble dyes which cannot be eliminated by acid, hence the term Acid-fast. Acid fastness is not a property exclusive of M. tuberculosis; non-tuberculosis mycobacteria (Table 6), rhodochrous, norcardia and pitsburgh pneumonia agent can be stained acid fast (68).

Mycobacteriun tuberculosis possesses a thick lipoidal wall which has a dual effect. First the wall renders the organism impermeable, protecting it from adverse environment such as that found within the phagocytes or within tissues containing a drug or antibody. Second, the cell wall component participates in induction of certain activities, some of which are helpful to the host in its effort to contain progression of disease, some cause tissue destruction and others involve both. The component of the bacilli are:-

(a) Whole cell
(b) Wax D
(c) N - Glycolyl maramyl dipeptide
(d) Cord factor
(e) Sulfatide
(f) Phthienoic acid and mycocerosic acids
(g) C - Mycoside

The effects of these components could be:-

(a) Granulomagenic
(b) Macrophage activation
(c) Toxicity
(d) Increase host resistance
(e) Adjuvant activity
(f) Lysosome dysfunction
(g) Mycrobial shield

Toxicity, lysosome dysfunction and mycrobial shielding are responsible for the virulence of the organisms. Sulfatides prevent the release of lysosomal enzymes in the phagosomes, the oc-mycoside forms a shield around the organism and cord factor is toxic to tissue (65).

PATHOGENESIS AND PATHOLOGY

The disease is spread from person to person by droplet infection. The source of infection being persons with open tuberculosis. Hence the spread of infection is facilitated by overcrowding and poor socio-economic status. The source of reservour varies widely in different parts of the world, from about 7% in the USA to essentially the whole adult population in certain countries in Africa, Asia and South America (65). There are two types of tuberculosis:- (a) primary TB common in children and (b) secondary or adult tuberculosis which could be due to reactivation of an indolent primary focus or is due to re-infection. Where an infected droplet nucleus is deposited in the alveolus of a susceptible person, a non-specific asymptomatic bronchopneumonia - the primary Ghon's focus develops. Tubercle bacilli from the primary focus drain to the regional lymph node and the combination of the two form the Ghon Complex. Subsequently, lymphatic drainage delivers tuberculosis bacilli to the systemic circulation and then potentially to all organs of the body (66,68). In about 5% of newly infected persons, the primary process progresses and becomes radiologically and clinically apparent tuberculosis disease (69). Rarely, the lymphohaematogenous spread of a large number of bacilli throughout the body may lead to miliary tuberculosis or extrapulmonary manifestations. It is estimated that about 15% of tuberculosis is extrapulmonary (69). By far the commonest outcome of the initial infection with M. tuberculosis is healing with granuloma formation. In most stable persons the healed granulomas remain stable and with time calcify; overt disease never occur. In about 5 - 15% of cases one of the granulomas in the lungs or elsewhere in the body - breaks down and tubercle bacilli are spread and the person becomes ill with tuberculosis (65,69).

Tuberculosis is an example of specific chronic inflammation characterised by granuloma foreation. The granulomata are induced by granulomagenic substance of the tubercle bacilli or by the immunological responses to the antigen (65). Boro D L reviewed granuloma disease and pointed that such lesions are usually sharply demarcated from surrounding tissue cells. The cell composition was reported to be in a dynamic state, and varied throughout the stages of formation and involution. At the height of a granulomatous response, T cells predominate although B cells would be present. The macrophages are abundant and continue their phagocytic,

effector and affector roles in the immune response. Some of these cells may be transformed into epithelioid cells which are less phagocytic but active in the elaboration of enzymes. Eventually, some of the macrophages may form multinucleate giant cells. The function of neutrophils which are present in the earlier stage of granuloma formation is in the liquifarction of the caseous material (65).

TUBERCULO-IMMUNITY

For many years the cellular and humoral immunity induced by M. tuberculosis has served as a valuable model. All immune activities are dependent on the lymphocytes both T-cells and B-cells. The role of B-cells in immunity of tuberculosis is not clear. However, it has been reported that they may produce lymphokines such migration inhibitory factor (MIF) which affect macrophage activity and this contributes to immunity in a manner similar to T cells (65). Bona et al has suggested that B lymphocytes might also exert some suppressive influence on T cells. However, the suppressor population appear to consist of monocytes. The T4-helper lymphocytes are the cell type most associated with protective immunity in tuberculosis. The positive effect of T4-helper cells is countered by suppressor monocytes and T8 suppressor lymphocytes. In early tuberculosis, the T4-cells are prominent whereas in advanced disease and in the presence of a large bacterial load, the suppressor influence is more prominent (65). Kleinhenz and Ellner showed that in tuberculosis adherent monocytes and T cells with specific receptor for the FC position of lgG. (T) independently suppressed responsiveness to specific antigen and thus contribute to anergy. The interaction of immune T4 lymphocytes with tubercle bacilli or antigen result in the release of a number of mediators (lymphokines) with different activity (Table 7). Those mediators which mobilize and activate macrophages are the most important in the destruction of tubercle bacilli and recovery from the disease. Macrophage chemotactic factor is responsible for the movement of macrophages to the site of tubercle bacilli. Macrophages so attracted are encouraged to remain at the site by migration inhibitory factor (MIF). Increased enzymic activity is induced by macrophage activating factor. Blastogenic factor directs the activity

of lymphocyte by inducing proliferation and further participations of the new cells in various reactions. Transfer factor can impart tuberculin sensitivity to non-sensitive cells.

DIAGNOSIS

Although the history, physical examination, skin test data and other studies such as X-rays are frequently helpful adjuncts and at times may strongly suggest tuberculosis, definitive diagnosis requires the demonstration of M. tuberculosis in the patients' tissues or fluids by microscopy and culture (30,65,69). The acid-fast stain remains a valuable technique for rapidly establishing presumptive diagnosis of tuberculosis. In addition the close correlation of the positivity of sputum smears with infectiousness makes the technique a valuable adjunct in the general management and contact investigation of a case of tuberculosis (27,69). Although the demonstration of acid-fast bacilli inexpectorated sputum remains the most important test for establishing the diagnosis of tuberculosis, sputum smears may be unreliable. Between 22 and 66 percent of the patients with tuberculosis have negative smear and positive culture (27). In a recent study (70), 26% of the patients with proved tuberculosis had persistently negative examination of sputum. The authors observed that it is not unusual for sputum studies to be negative in patients with closed tuberculosis. They also observed that in order to identify tubercle bacilli in microscopical examination of a smear, 10^4 organisms must be present. Their conclusion was that the examination of sputum is negative in 60-80% of patients with minimal to moderately advanced non-cavitating tuberculosis and in 30 to 40% of patients with more advanced disease.

Culturing M. tuberculosis is more expensive and time consuming than acid-fast staining procedure and yet it is essential for distinguishing M. tuberculosis from other mycobacteria and for testing drug sensitivity. Blair E B et al (71) noted that culture is more sensitive than smear in detecting the presence of mycobacteria and that smear and culture techniques were complimentary. Several weeks to months may be needed

before culture can be read as positive, and this may delay diagnosis, treatment and drug susceptibility testing. Recently Odhma G et al (72) described a technique that uses gas CHROMATOGRAPHY and Mass SPECTROMETRY to identify tuberculostearic acid in sputum cultures after only 5 days of incubation which represents an exciting experimental approach to this problem. Other diagnostic tests will be discussed under Tuberculosis and AIDS or HIV infection.

TREATMENT

Initially the drugs were used alone and for a short period of time. This regime had its disadvantages (29). First, many patients particularly those with extensive disease had their sputum positive for a long time. Secondly, the organism harboured by these patients often became resistant to the drugs being used. Subsequent studies by the British Medical Research Council (1962) revealed that multiple drug regimes of longer duration had improved effect.

Thus it became a standard practice for patients to receive multiple drugs for 18 to 24 months. Unfortunately, this long duration of treatment created other problems such as poor patient compliance, high cost, and logistic difficulties in delivering services (69,73,74). These problems were especially severe in developing countries where they posed major obstacles to the successful completion of therapy (69). Several studies were therefore undertaken - in developing nations to look into the drug regime that might permit short duration of treatment and still produce high rate of cure. An example of such studies is the East African/British Medical Research Council controlled trial in which Zambia was an active participant (73,74). As a result of such studies, Zambia has adopted the 8 month regimen during which streptomycin, thiacetazone, Isoniazid, Rifampicin and Pyrazinamide (STHRZ) are given on daily basis for 2 months followed by Thiazina for 6 months in sputum positive patients over the age of 16 years. For patients under 16 years who are sputum positive, Steptomycin, Thiazina are given for 2 months followed by Thiazina for 10 months (Ministry of Health Circular No. MH/103/4/11). The relapse rate

during the 5 drug regime is 4% whereas that for 3 drugs regimen is 3%. The differences between these figures is insignificant. The relapse rate in defaulters is 10%. The short course regimens, however, cannot yet be recommended for treatment of extrapulmonary tuberculosis or for pulmonary disease in patients with complicating medical problems such as diabetes mellitus that may alter the response to therapy.

TUBERCULOSIS AND AIDS AND HIV INFECTION

Tuberculosis is a common opportunist in AIDS (20,23,27,67,75,76). It is reported to be common in AIDS patients native for the tropics than the temperate (20). However, atypical mycobacteriosis does occur in patients with AIDS native to the developed nations (20). In a review of 446 patients with AIDS, 55 tuberculosis, of whom 9 were Africans (5 Africans in Europe and 4 native Africans) (20). Among the Caribbeans living in America or Europe and natives the figures of tuberculosis were 23 and 17 cases respectively (20). Quinan M E et al (77), hypothesized that the manifestation of disease among the risk groups may depend on the groups previous exposure to infectious agent. In a recent study of 82 AIDS patients; 45 Haitians and 37 non-Haitians had tuberculosis (23). Of the 27 Haitians with tuberculosis, 19 had extrapulmonary tuberculosis whereas only 56 of 286 Haitians with tuberculosis without AIDS had extrapulmonary (P 0.0001). Tuberculosis preceded the syndrome by 1 to 17 months in 20 patients with the syndrome (23). In the above study, the frequency of disseminated atypical mycobacteriosis or positive sputum cultures for atypical mycobacteriosis was not significantly different between Haitians (11.3%) and non-Haitians (8.3%) patients with the syndrome (23). In another study on Haitians with tuberculosis (2 pulmonary and 9 extrapulmonary), 7 developed AIDS (67). Of these 7, 4 were HIV seropositive at the time of tuberculosis while the other 3 were HIV seropositive at the time of AIDS. Still among the Haitians, of 10 patients with AIDS, 6 had tuberculosis (22).

Disseminated infection due to mycobacteria tuberculosis has been reported in AIDS (25). Bacteraemia in the disseminated mycobacteria tuberculosis

is rare. However, bacteraemia due to mycobacteria tuberculosis in a 45 years old drug addict male has been described (25). On the contrary, bacteraemia is common in disseminated mycobacterium avium intracellulare in AIDS patients (24,28,77,78). Between 1979 and April 1983, of the 18 African patients diagnosed as having AIDS, in Europe two had tuberculosis (1 pulmonary and 1 tuberculosis lymphadenitis) (9). In Rwanda (Kigali), of 26 patients reported with AIDS in 1983, 3 had tuberculosis (two localised to the lungs; one disseminated) (14). In Uganda, out of 8 patients admitted to the tuberculosis wards and HIV seropositive, 4 had positive sputum for acid-fast bacilli (55). In Zambia, it has been reported that 17 (24%) out of 71 patients with tuberculosis were seropositive to HIV antibody (11). In Zaire, 53 (33%) of 159 confirmed pulmonary patients hospitalized in a tuberculosis sanatorium were HIV seropositive, including 10 (67%) of patients with extrapulmonary tuberculosis (75). Seropositivity was significantly associated with age 20 - 29 years, anergy to intradermal injected tuberculin, and with a blood transfusion during the previous 5 years. Among these patients, there was no significant association between HIV infections and extent of radiographic lesions, Duration of disease or initial response to treatment (75). In a study of 45 Haitians with AIDS and tuberculosis, 10 patients were treated with conventional antituberculosis drugs and the culture results became negative within 1 to 4 months and tuberculosis did not recur during a follow-up of 3 to 18 months (23).

The diagnosis of tuberculosis in AIDS also depends on history taking, physical examination and on the demonstration of M. tuberculosis in patients' tissue and body fluids by Microscopy and culture (23). Other investigations, for example fibreoptic bronchoscopy and transbronchial lavage and biopsy are reported to be helpful in the diagnosis of opportunistic infections in AIDS patients (79). The diagnostic yield increases when bronchoalveolar lavage and transbronchial biopsy are combined (79). For example bronchoalveolar lavage and transbronchial biopsy had sensitivities of 86% and 87% respectively in 276 fibreoptic bronchoscopic examination in 171 patients with known or suspected AIDS (79). Other investigations are blood culture and fecal examination (24). Between February 1981 and February 1984 at Memorial Slaon Kettering Cancer

Centre, 301 patients with AIDS mycobacterium avium were diagnosed by blood culture and acid-fast stain and culture of fecal specimens (24). The role of ultrasonography in the diagnosis of tuberculosis is still limited. Nevertheless, Abiri M Metal (1985) reported the use of ultrasonography in detecting extrapulmonary tuberculosis in 3 cases (80).

The findings on chest radiographic appearance are best demonstrated in a study of 23 tuberculosis patients: 17 pulmonary and 6 extrapulmonary (81). In 17 patients the radiographs revealed hilar and/or mediastinal adenopathy in 10 patients (59%), localised pulmonary infiltrates limited to the middle or lower zones in 5 patients (29%), localised pulmonary infiltrates involving the upper zone in 3 patients (15), diffuse miliary or interstitial infiltrates in 3 (18%), no pulmonary infiltrate in 6 patients (35%) and no abnormalities in 2 patients (12%). Pulmonary cavitation was not seen. Only one patient (6%) had a chest radiograph typical of adult onset reactivation tuberculosis (ie. localised pulmonary infiltrate involving the upper lung fields with hilar or mediastinal adenopathy). Six patients (35%) had pulmonary infiltrate that may have been caused by concomitant non-tuberculosis. Of the six extrapulmonary tuberculosis, 3 patients (50%) had hilar and/or mediastinal adenopathy.

CHAPTER 3

PATIENTS AND METHOD - BACKGROUND

Zambia has a population of 5.7 million (1980 census) of whom 2.3 million are urban and 3.4 million are rural. Lusaka is the capital city with a population of 538,469 (1980 census). The University Teaching Hospital (UTH) is the city's only hospital with a capacity of 1,000 beds and sees patients from the city and referrals from hospitals all over the country. St. Francis Hospital, the second General Hospital in Eastern Province of Zambia has a capacity of 300, beds. The hospital was run by the Anglican Mission until August 1986, when it became a joint venture between the Anglicans and the Catholic Church. It is the only hospital in Katete Boma with a population of 10,000 and Katete District with a population of 94,208 (1980 census).

RESEARCH DESIGN

This was a matched case control study undertaken in the University Teaching Hospital (urban) and St. Francis Hospital (rural) from May 1986 to February 1987.

SELECTION OF PATIENTS

Patients with confirmed diagnosis of tuberculosis admitted to the TB Ward of St. Francis Hospital, and attending the Chest Clinic of UTH who consented verbally and between the ages of 15 and 70 years, were automatically included in this study. The age limits were chosen because 80% of the TB cases in UTH in 1985 fell within the age group. The diagnosis of TB was confirmed by a positive sputum for acid-fast bacilli and by positive histopathology from the Pathology Laboratory at the University Teaching Hospital. Patients with pleural effusion were deliberately included in this study although no acid-fast bacilli could be

seen in the pleural aspirate because our experience showed that TB was the commonest cause of effusion and most of the patients responded well to the conventional anti-tuberculosis chemotherapy. Nevertheless, the principal investigator was aware that other diseases particularly Pneumocystis carinii complicating HIV infected persons may present with an effusion. All patients were seen and examined by the principal investigator.

In St. Francis Hospital (Katete), the Ziehl-Neelsen staining of sputum and the reporting were done by one of the senior Laboratory Technicians. However, a second specimen of sputum was sent to the TB Laboratory in Chelston, Lusaka for repeat Ziehl-Neelsen (ZN) staining, culture and sensitivity to the mycobacterial isolate. On the other hand all UTH sputum were sent to TB Laboratory - Chelston, for ZN staining, culture and sensitivity and stain identification of the mycobacterial.

Patients with suspected TB lymphadenitis had their enlarged lymphnodes biopsied, and specimens sent to UTH Pathology Laboratory for Histopathology. Here, one of the Senior Pathologists who is also interested in Histopathology in AIDS, reported on the specimens. However, special staining of tissues for acid-fast bacilli and tissue culturing were not done.

CONTROLS

These comprised blood donors, persons seeking medical examination, in-patients and out-patients. The blood donor and individuals who came for medical examination were considered healthy as they had no symptoms suggestive of either TB or AIDS. The in-patients and out-patients were entered in the study if they had neither TB nor AIDS. All the controls gave verbal consent. These controls were matched with patients for age sex and two controls were selected for each patient.

DATA COLLECTION

All the data was collected by the principal investigator. The information concerning personal characteristics, clinical presentation of TB and the diagnostic test used to confirm the diagnosis and the drugs used were entered on questionnaire.

SEROLOGY

KATETE: 10 mls of blood was collected from patients and controls by venipuncture. The blood was centrifuged, sera collected and stored frozen at - 20°C (after being properly labelled) until when all sera had to be transferred to UTH (Lusaka) in cooler boxes.

UTH: 10 mls of blood was collected and sent to the Immunology Laboratory where centrifuging was done, sera collected and stored at - 20°C until when testing was done.

All sera in the two study groups was tested for the presence of antibodies against HIV by using a specific competitive enzyme linked immunosorbent assay (ELISA) as described (33).

TEST PROCEDURE OF WELLCOZYME ANTI-HTLV-III

1. Mix Anti-HTLV-III lgG from a British patient and Horseradish peroxidase (HRPO) in a ratio of 3 HRPO:1 lgG.

2. Mix 25UL of test serum and 75UL of the optimum dilution of HRPO-anti-HTLV-III in wells coated with crude antiglobulin also prepared from a high anti-HTLV-III titre sera from a British patient.

3. Incubate for 1 hour at 45°C.

4. Wash with saline containing 0.1% tween 20.

5. Aspirate to dryness.

6. add 100UL Tetramethylbenzidine in citrate/acetate at PH 6.0 + 0.003% H_2O_2.

7. Leave for 20 minutes.

8. Stop the reaction by adding 2 mol/L sulphuric acid.

9. Do colour measurement spectrophotometrically, at 450nm.

10. All sera whose reaction is stopped by sulphuric acid by 50% or more contain antibodies against HIV and hence are seropositive.

WEIGHTS

As a variable used as a determinant to response to TB chemotherapy all TB patients in St. Francis Hospital were weighed weekly by using the flat portable scale. These weights were recorded in Kg body wt.

DATA ANALYSIS

HIV seropositivity correlation between patients and control was done by the use of Mantel - Haenszel matched Chi-squares for multiple controls. To determine whether there was any difference in wt. gains between seropositive TB patients and seronegative TB patients as controls the students, T-Test (two tailed) was employed. The Chi-square for trend was employed in the analysis to check whether seropositivity increased with age or not.

CHAPTER 4

RESULTS

A total of 72 patients (32 patients Katete and 40, UTH) entered this study. Their mean age was 31.6 and range 15-60 years old. There were 26 males (16 UTH and 10 Katete) and 46 females (24 UTH and 22 Katete). There were 144 matched controls (64 Katete plus 80 UTH) for age and sex.

Of the 72 patients, 31 (43%) cases had antibodies against HIV as compared with 15% seropositivity among controls (P value 0.000001 and odd ratio of3). Eight patients (25%) of the 32 patients seen in Katete were seropositive compared with only 6.2% of the controls who were seropositive (P value 0.0073 and an odd ratio of 2). Twenty three (57%) cases of 40 patients in UTH had antibodies to HIV compared with 22.5% seropositivity among the control group (P value 0.00002 and odd ratio of 4). The data shows that the incidence of HIV infection characterised by seropositivity is higher among TB patients than among controls. The differences between patients and controls are highly significant. The data also revealed that the incidence of seropositivity is higher both in patients and controls in UTH than the patients in Katete. The chances of being seropositive among UTH tuberculosis patients are four times greater than the controls (Odd ratio 4) whereas the chances of being seropositive among the Katete tuberculosis patients is only two times greater than the controls. On the overall, TB patients are three times more likely to be HIV seropositive than the age, and sex matched controls.

TABLE 8 - HIV Seropositivity, in the different clinical types of tuberculosis in Katete and Lusaka patients.

CLINICAL TYPE	TOTAL NO	SEROPOSITIVE	
		NO	PERCENT
PTB	54	17	31.5
TB Lymphadenitis	9	8	88.9
Pleural Effusion	7	5	71.4
TB Peritonitis	2	1	50.0
TOTAL	72	31	43

Although there were more patients with pulmonary tuberculosis 54/72 than there were extrapulmonary patient 18/72, the incidence of HIV seropositivity was higher among the latter than the former (See Table 8). Of the 18 patients with extrapulmonary tuberculosis 8/9 TB lymphadenitis were seropositive and 5/7 pleural effusion were seropositive. Hence the chance of a patient with TB lymphadenitis becoming seropositive is higher than in all the other clinical types of tuberculosis.

The 40 patients from UTH and their controls were evaluated to see whether seropositivity increases with age. The results indicate that there was no significant increase of seropositivity for HIV with increasing age. (P value 0.35). However, the incidence of seropositivity is higher between ages of 25 and 35 years old.

The weights of the TB seropositives from Katete were compared to TB seronegatives weights and analysis showed that the means of the two samples were not significantly different (P value 0.85). This suggests that the response to chemotherapy of seropositive tuberculosis patients is not different from seronegative TB patients.

CHAPTER 5 - DISCUSSION, CONCLUSION AND RECOMMENDATIONS

DISCUSSIONS

Although one would have expected diseases such as tuberculosis in which the host depends on cell-mediated immunity for the control of the disease, to be common and overwhelming in patients with AIDS, there has been surprisingly few reports of such cases (23,76,81). In the USA, the majority of patients with AIDS and tuberculosis are immigrants from Haiti (82) and perhaps it is for this reason that the Centre for Disease Control specifically excluded tuberculosis as an AIDS diagnostic criterion. In Africa, particularly Zambia, there has not been any study on AIDS and tuberculosis, the majority of the data are isolated and incidental. They are incidental because the investigation met tuberculosis in the process of looking for other things. In this study, I have tried to look at HIV infection and tuberculosis. The total number of 72 confirmed cases of tuberculosis described here may seem to be few but they are representative of tuberculosis because they have been carefully selected and controlled.

My data shows that the overall seropositivity to HIV among tuberculosis patients is 43%, versus 15% seropositivity among the controls. Recently, Melbye M et al (11) reported 24% of seropositivity in 71 patients with tuberculosis in his review of seropositivity of HIV in 1,078 subjects in Lusaka, Zambia. Unfortunately, comparison of these results may not be easy because different methodologies were used. Furthermore, we do not know whether his TB (tuberculosis) patients were confirmed or not since it has been known that many patients attending the Chest Clinic and receiving anti-tuberculosis chemotherapy are actually not confirmed either by Ziehl-Neelsen or culturing. My results are closer to Mann J et al figure of 33% seropositivity of 159 confirmed tuberculosis patients in Kinshasa, Zaire (75). The peak incidence of seropositivity in the present study was between the ages of 22 and 35. This suggests that HIV infection is more prevalent among the sexually active individuals, which confirms other reports that HIV in Africa is transmitted heterosexually (11,13,14,52). The urban study group has a higher incidence of seropositivity to HIV than the rural group. These figures suggest that the HIV infection is new in

Zambia and that the epidemic has started in the urban area and is just spreading to the rural area. This is in disagreement with earlier reports that AIDS and HIV infection might have been in existence, in Africa for centuries, perhaps in the remote areas where Green monkeys are said to be in close proximity to the Human population (25,27).

My findings are in agreement with earlier reports (45) that HIV seropositivity is rare in the rural areas. Extrapulmonary tuberculosis was found to have the greatest incidence of seropositivity. Others have reported the same (23,67,76).

This data shows that histology can be used in the diagnosis of M tuberculosis in HIV infected individuals. Suddarum E et al (76) reported that 29 of 43 biopsies, were positive for M tuberculosis on histology. In the same study, only 3 of 43 biopsies showed no granuloma even though M tuberculosis was isolated. They further demonstrated that 8 of 17 patients from whom biopsies were taken showed necrotising granuloma and 6 of 17 patients showed no necrotising granuloma. The granuloma formation is not peculiar to M tuberculosis, other mycobacteria eg. Mycobacterium avium intracellular (MIA) also form granuloma. For example, 13 of 22 biopsies taken from 19 patients with MIA showed granuloma formation, 2 rare granuloma, 5 non-necrotising granuloma and none had necrotising granuloma. These findings tend to confirm Jagadha V et al conclusion that normal values of lymphocytes are not necessary for granuloma formation.

Up to the present moment there are no reports to show that patients with HIV infection or AIDS and Tuberculosis respond unfavourably to the standard anti-TB chemotherapy (23,76). My data shows that comparison of the weight gains of seropositive TB and seronegative TB patients showed insignificant difference. Therefore seropositive TB patients should not be denied treatment as they respond equally well to chemotherapy. Many methods used in the diagnosis of tuberculosis in AIDS have been described (24,79,80). In this study the methods were limited to ZN staining of sputum for Acid-fast bacilli and culture and sensitivity. Even the culture method was not being used to full capacity due to lack of reagents. This lack of diagnostic tools may result in either under-estimation or over-estimation.

Lack of facilities led to the inability to identify the type of strain of mycobacterian. Consequently, I am unable to report on the number of atypical non-tuberculosis mycobacteriosis.

Finally, there is no report in the literature of Steven Johnson Syndrome in HIV infected patients with tuberculosis, a condition that has been described in Zambia Hira S K, personal communication). The only reaction reported in the literature is drug to drug interaction of Ketoconazole and Rifampicin in a patient with AIDS and Tuberculosis, and severe oesophageal candidiasis (83).

CONCLUSION

HIV infection is a new epidemic in Zambia affecting the young age group who are sexually active. HIV infection is slowly spreading to the rural area. There is a strong association between HIV infection and tuberculosis. Since tuberculosis is endemic in Zambia and that HIV infection is thought to reactivate latent tuberculosis infection, a great number of seropositive will have tuberculosis. The annually increasing number of tuberculosis reported in UTH since 1980 (P value 0.000003) may be a manifestation of HIV infection similar to that seen in certain cities in the USA (29).

RECOMMENDATION

Tuberculosis is a health problem in Zambia and so is the epidemic of HIV infection and AIDS.

There are many areas for future research. To better understand the problem and to design the most effective and efficient programme, strategies, it will be essential to establish:-

(a) The relative risk among persons with both tuberculosis infection and HIV infection of developing clinical tuberculosis compared with suitable control with tuberculosis infection.

(b) Whether patients with HIV infection and tuberculosis are more likely to transmit tuberculosis infection to others.

(c) The proportion of tuberculosis patients who have AIDS.

(d) The efficacy of current treatment regimens among patients with HIV infection and tuberculosis by doing longitudinal studies.

(e) The tuberculosis morbidity caused by HIV infection.

Before we have answers to the above, it is recommended that Doctors and Public Health Workers in Zambia and developing countries where tuberculosis is a common disease should be aware of the association between HIV infection and tuberculosis.

TABLE 1 Provisional World Health Organisation (WHO) clinical case definition for AIDS where diagnostic resources are limited. Definition developed at the WHO workshop on AIDS in Bangui, Central African Republic.

ADULTS: AIDS in an adult is defined by the existence of at least two of major signs associated with at least one minor sign; in the absence of known causes of immunosuppression, such as a cancer or severe malnutrition or other recognised aetiologies.

MAJOR SIGNS:
(a) Weight loss > 10% of body weight
(b) Chronic diarrhoea > one month
(c) Prolonged fever > one month (Intermittent or consistent

MINOR SIGNS:
(a) Persistent cough for one month
(b) Generalised pruritic dermatitis
(c) Recurrent herpes zoster
(d) Oropharyngeal candidiasis
(e) Chronic progressive and disseminated herpes simplex infection.
(f) Generalised lymphadenopathy

NB. The presence of generalised KS or cryptococcal meningitis are sufficient by themselves for the diagnosis of AIDS.

CHILDREN: Paediatric AIDS is suspected in an infant or child presenting with at least two major signs associated with at least two minor signs in the absence of known causes of immunosuppression.

MAJOR SIGNS:
(a) Weight loss or abnormally slow growth
(b) Chronic diarrhoea > one month
(c) Prolonged fever > one month

MINOR SIGNS:
(a) Generalised lymphadenopathy
(b) Oropharyngeal candidiasis
(c) Repeated common infection otitis pharyngitis
(d) Persistent cough for one month
(e) Generalised dermatitis
(f) Confirmed maternal LAV/HIV infection

TABLE 2 - IMMUNOLOGIC ABNORMALITIES IN AIDS

I. Abnormalities that characterise the syndrome:-

(1) Lymphopenia.

(2) Selective T cell deficiency based on a qualitative reduction within the antigenic subset designated T4 or leu - 3 monoclonia antibodies.

(3) Decreased or absent delayed cutaneous hypersensitivity to both recall and new antigens.

(4) Elevated serum immunoglobin predominantly 1gG., and LgA., in adults and 1gM. in children.

(5) Increased spontaneous immunoglobulin secretion by individual B lymphocytes.

II. Consistent observed abnormalities:-

(1) Decreased in vitro lymphocyte porliferative response:-
(a) Mitogen
(b) Antigen
(c) Allocatigen, autoantigen

(2) Decreased cytotoxic responses:-
(a) Natural killer cells
(b) Cell mediated cytotoxicity T cell

(3) Decreased ability to mount a de nove antibody response to a new antigen.

(4) Altered monocyte function.

(5) Elevated serum levels of immune-complexes.

III. Other reported abnormalities:-

(1) Increased levels of acid labile and interferon.

(2) Antilymphocyte antibody.

(3) Suppressor factor.

(4) Increased levels of B - 2 immunoglobulin and 21 thymulim levels.

TABLE 3 - CASES OF TUBERCULOSIS REPORTED TO THE CENTRE FOR DISEASE CONTROL (CDC) - USA

YEAR	TOTAL CASES	DEATHS	CASES PER 10^6	CASES PER 10^6
1977	30145	2968	13.1	1.4
1978	X	X	X	X
1979	27699	X	X	X
1983	24394	X	X	X
1984	22255	X	9.4	X
1985	21801	X	9.1	X

X - STATISTICAL FIGURE NOT REPORTED

TABLE 4 - ANNUAL DECLINE OF REPORTED TUBERCULOSIS IN USA - CDC

YEAR	AVERAGE ANNUAL DECLINE
1975 - 1978	5.7%
1978 - 1981	1.5%
1982 - 1984	6.7%
1984 - 1985	2.0%

UNIVERSITY TEACHING HOSPIITAL

MEDICAL RECORDS/STATISTICAL DEPARTMENT

CASES OF TUBERCULOSIS, 1981 - 1985 (5YEARS)

TYPE OF TUBERCULOSIS	1981		1982		1983		1984		1985		FIVE YEAR MOVING TOTALS	
	DIS-CHARGE	DEATH	DIS-CHARGE	DEATH	DIS-CHARGE	DEATH	DIS-CHARGE	DEATH	DIS-CHARGE	DEATH	DIS-CHARGE	DEATH
PLEURAL EFFUSION AND PULMONARY TUBERCULOSIS	784	64	875	100	979	116	965	128	1,250	200	4,853	608 P=0.000003
TUBERCULOSIS OF INTESTINES AND PERITONITIS tuTUBERCULOSIS	26	8	24	8	40	3	42	5	53	9	185	33 P=0.118
TUBERCULOSIS OF BONES AND JOINTS AND ARTHRITIS	214	2	261	7	236	5	239	4	207	4	1,157	22 P=0.795
TUBERCULOSIS OF LYMPHODENITIS INCLUDING LATE EFFECTS	14	4	18	2	29	6	15	5	18	2	92	19 P=0.748
SUB TOTALS	1,038	78	1,178	117	1,284	130	1,259	142	1,528	215	6,287	682
ANNUAL TOTALS	1,116		1,295		1,414		1,401		1,743		6,969	

CH1 - SQUARE FOR TRENT.

TABLE 6 - MYCOBACTERIA CAPABLE OF CAUSING HUMAN DISEASE

PRINCIPALLY PULMONARY

M Tuberculosis - Africaum bovis complex
M Asiaticicum
M Avium / M intracellulare
M Kamsasii
M Malmiense
M Simiae
M Szulgae
M Xeropi

PRINCIPALLY SKIN

M Leprae
M Ulcerans
M Marinum
M Chelonei (also an implant)

PRINCIPALLY LYMPHOID

M Scrofulaceum
M Hemophilum

TABLE 7 - FACTORS RELEASED BY ACTIVATED LYMPHOCYTES

INHIBITORS OF GROWTH

- Proliferation inhibitory factor (PIF)
- Clonal inhibitory factor
- Cytotoxic factor

PROMOTERS OF GROWTH

- Blastogenic factor

INHIBITOR OF MOTILITY

- Migrationinhibitory factor (MIF)
- Leukocyte (Polymorphonuclear) Inhibitory factor (LIF)

PROMOTERS OF MOTILITY

- Chemotaxin

ACTIVATOR AND INFLAMMATORY INDUCER

- Macrophage activating factor (MAF)
- Skin reactive factor (SRF)

TRANSFER FACTOR

- (Interferon)
- (Antibody)

HIV ANTIBODY AMONG TUBERCULOSIS PATIENTS IN ZAMBIA

1. PERSONAL CHARACTERISTICS

Name: Age: Sex:
File No: Hosp: Word:
Educational Status:
No Education/Primary/Secondary/University/College
Residential Area/Village Town/Chief

2. CLINICAL PRESENTATION

2.1	a)	Cough	Yes/No Duration	Dry/Productive
	b)	Sputum	Purulent Blood stained Others	Yes/No Yes/No
	c)	Fever		
	d)	Night Sweats		Yes/No
	e)	Weight loss	< 5kg > 5kg	10kg
	f)	Lymphadenopathy:		
		Cervical		Yes/No
		Axillary		Yes/No
		Inguinal		Yes/No
	g)	GIT:		
		Abdominal pain		Yes/No
		Vomiting		Yes/No
		Mass		Yes/No
		Diarrhoea		Yes/No
	h)	CNS:		
		Headache		Yes/No
		Nechache		Yes/No
		Do your hands shake?		
		Is your memory as good as usual?		

2.2 PHYSICAL EXAMINATION

a) General
- i) Fever
- ii) Weight loss
- iii) Lymphadenopathy
  - Cervical Lt R Bill Discrete/Matted
  - Axillary Lt R Bill Discrete/Matted
  - Inguinal Lt R Bill Discrete/Matted

b) RS
- i) Chest Symmetrical Asymmetrical
- ii) Movements
- iii) Trachea Central Shifted RtELt
- iv) Percussion note Resonant Impaired Stony Dull
- v) Breath sounds Vesicular
- vi) Crepitations Fine/Coarse

c) Abdomen
- i) Distension
- ii) Tenderness
- iii) Guarding
- iv) Fluid Thrill
- v) Masses: Liver, Spleen, Others

3. INVESTIGATIONS

	Before Rx	After Rx
a) SPUTUM for AAFB		
i) Ziehl-Neelsen Stain	Pos/Neg	Pos/Neg
ii) culture	Pos/Neg	Pos/Neg
iii) Strain for Mycobacteria Tuberculosis hominis, Avium intracellulare, Others		

*b) C X R PA view
- i) No pathology
- ii) Snow-storm appearance
- iii) Patchy consolidation
- iv) Lobar consolidation
- v) Lung collapse
- vi) Cavitating
- vii) Others

c) LYMPH NODE Biopsy Report Positive/Negative

d) Serological Rest for ~~HTLV-III~~ HIV Antibody
- i) ELISA Positive/Negative
- ii) W B Positive/Negative

4.** TREATMENT

a) Streptomysin
b) Isoniazid
c) Thiazina
d) Ethambutol
e) Rifampicin
f) Pyrazinamide

* Tick ( ) against the radiological finding

**Put a tick ( ) against the drug to show which one the patient is on

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