THE IMPACT OF HUMAN IMMUNE DEFICIENCY VIRUS ON MENINGITIS IN ADULT ZAMBIAN PATIENTS

BY

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DECLARATION

I DR. FRIDA SAKALA KAZEMBE do hereby declare that this work is original and was done through my own effort. I also declare that this dissertation shall be the property of the UNIVERSITY OF ZAMBIA and that no part of this dissertation shall be published without prior permission from the UNIVERSITY OF ZAMBIA.

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APPROVAL

This dissertation of **Dr. FRIDA SAKALA-KAZEMBE** has been approved as a fulfilling part of the requirements for the award of the degree of Master of Medicine by the University of Zambia.

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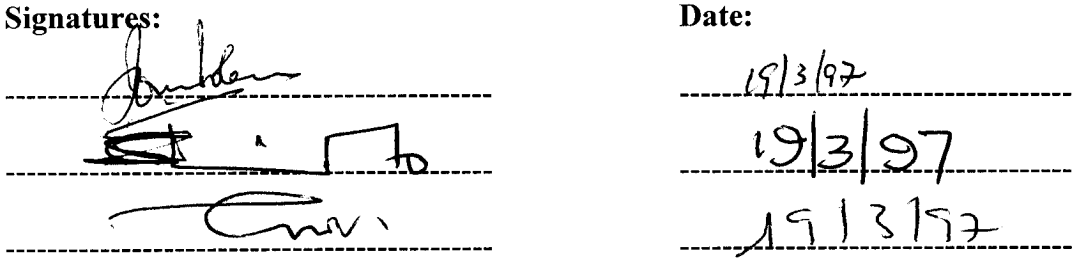

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DEDICATION

This dissertation is dedicated to my Late Loving Father, Rev. Nathan Thomas Mwanza, My Mother, My Husband and My Children.

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ABSTRACT

This is a clinical and laboratory comparative study of the clinical presentation and outcomes of Meningitis in 75 adult Zambian patients, 44 HIV positive patients (28 males and 16 females) and 19 HIV negative(10 males and 9 females) and 12 (7 males and 5 females) whose serostatus was not known, who were admitted to the University Teaching Hospital with a diagnosis of Meningitis during a period of four months beginning 1st December 1993 ending March 31 1994.

The study was prompted by the observation by the researcher of the appearance of a large number of patients who presented with fulminant meningitis associated with severe complications and a high fatality rate in the University Teaching Hospital in the cold season of 1992.

The major objectives of the study were:-

(1) To determine the prevalence clinical and epidemiological features of meningitis in the presence of a Human Immune -deficiency viral infection epidemic.

(2) To establish whether or not there is a significant relationship between meningitis and Human Immunodeficiency Viral Infection

(3) To establish the common organisms causing meningitis in this environment

(4) To determine whether the management of Meningitis should be modified in a patient with HIV infection and

(5) Lastly to determine whether patients who have both meningitis and HIV infection develop more complications and to determine whether or not their outcome is different from that of patients who do not have HIV infection.

The Research Hypothesis tested was that "Meningitis has a fulminant presentation associated with greater complications and mortality in patients with HIV infections as compared to those who do not have HIV infection, on the assumption that:-

(a) HIV causes progressive deterioration of the immune system via both qualitative and quantitative dysfunction of CD4 T cells

(b) Autoimmune mechanisms and hyper function of the immune system associated with HIV infection may be associated with depletion of complement system.

All these mechanisms would then predispose patients who have HIV infection to (i) impaired cell mediated immunity (ii) impaired complement system function (iii) recurrent respiratory infections (iv) Bacteremia with encapsulated organisms.

All of which are high risk factors for fulminant meningitis, and therefore meningitis in HIV patients would then be expected to be a severe disease with severe complications as compared to meningitis in HIV negative patients.

The clinical presentation and outcomes of meningitis in HIV positive patients was compared with that of HIV negative meningitis patients and the following significant findings were noted:

1. Out of 75 patients (45 males 60% and 30 females 40% meningitis patients that participated in the study the serostatus results were received for 63 patients and the distribution was as follows:

44 (28 males and 16 females) were HIV positive and 19 out of 63 were HIV negative giving an over all sero positivity rate of 69% amongst the meningitis patients. The serostatus of 12 patients was not known.

2) The age range was 14 years to 79 with a mean age of 27 years, and 57% of the patients were aged below 40 years.

(3) Meningitis was found to be more prevalent amongst inhabitants of the high density areas i.e. 68 out of the 75 patients came from high population density areas.

(4) Pneumonia was found to proceed meningitis in 12 patients.

(5) The major clinical findings were a history of Headache 100%, fever 80% neckache 80% confusion 13.4% and the commonest physical signs, where neck stiffness in 100% patients, positive Kernigs sign and temperature.

(6) The average duration of symptoms before admission was 2 days. Both groups of patients came to hospital in the early stages of the disease.

(7) However, all those patients who had a history and physical signs of pneumonia on admission did not do well; of the 12 patients who had pneumonia + meningitis on admission 11 died (92%).

(8) Whereas the initial clinical presentation in the two groups did not differ significantly, the follow up, laboratory findings and outcomes in the two groups was statistically significant.
Severe manifestation such as hyperpyrexia 5/8, coma 5/7, seizures, confusional state, bleeding disorders, hemiplegia and 20/30 deaths, occurred more in HIV positive patients than in HIV negative patients, P value < 0.05.
The major causes of meningitis were not identified in that the majority of turbid CSF 50 out of 65 = 77% showed negative cultures. The 15 turbid CSF specimens that showed positive cultures yielded 9 cases Neisseria Meningitides 5 streptococcus pneumonia and 1 Salmonella species. 14 out of 65 (20%) were positive for cryptococcus neoformans and all the 14 occurred in HIV positive patients.

The mortality in HIV positive patients was much higher in that 26 out of the 30 deaths (86%) were HIV positive. The proportion of deaths in HIV positive patients was 26/44 = 59%.

All the above strongly supported the hypothesis that stated that meningitis in HIV positive patients is a severe disease associated with a significant number of complications and mortality than in HIV negative patients

1.0 INTRODUCTION:

Meningitis defined as inflammation of the meninges of the brain and spinal cord represents one of the major medical emergencies (ref ROOS K L,TUOMANEN ET AL and WENGER J D ET AL). It is a major cause of morbidity and mortality in developing countries (ref ROOS K L ,WENGER J D ET AL). It may be classified as acute or chronic, depending on the onset and duration of symptoms, and can be caused by: Bacteria, viruses, fungi,and Protozoa (ref ROOS K L ,BI DUERDEN ET AL).

Whatever the causative agent, clinical features are dominated by: headache, irritability, fever, and neck stiffness.

The above symptoms and signs are accompanied by nausea, vomiting photophobia and coma resulting from the raised intracranial pressure. Even though all the organisms listed above can cause meningitis, Bacterial Meningitis causes the major problems dominated by Neisseria Meningitidis, Haemophilus Influenza and Pneumo-coccal infections. This thesis will dwell on bacterial and cryptoccocal meningitis only, because facilities available can only diagnose Bacterial Meningitis, and Cryptococcal Meningitis.

1.1 DEFINITION:

Bacterial meningitis may be defined as an inflammation in response to bacterial infections of the pia-arachnoid and the fluid residing in the space which it encloses and also of the fluid in the ventricles of the brain and the space surrounding the spinal cord.(PATTERSON DAVID K ET AL TUOMANEN ET AL). Primary Bacterial Meningitis usually results from bacteremia and spread of bacteria to the meninges.

Bacterial meningitis is a medical emergency because despite modern anti-bacterial treatment, meningitis still carries significantly high morbidity and fatality rates (PATTERSON DAVID K ET AL, PHLLIPS ,TUOMANEN ET AL) and is associated with a multiplicity of neurological sequelae and defects especially if diagnosis and treatment are delayed (QUA GLIARELLO VINCENT ET AL,ROOS K L and TUOMANEN ET AL).

The CNS is an immune compromised organ which lacks any intrinsic lymph node lymphatic system akin to what exists in all other organ systems. The CSF Blood Barrier delay mobilisation of traditional host defence components, complement, antibody, and phagocytic cells hence microbes that gain access to the CNS compartment can multiply and invade nervous tissue and lepto meninges relatively unhampered by host defences during the initial phases of such infections (QUA GLIARELLON VINCENT,ROOS K L and TUOMANEN E ET AL).

1.2 ETIOLOGY:

The commonest cause of epidemic Bacterial Meningitis in adults in Zambia is Neisseria Meningitis, a gram - negative coccus found among the indigenous microbiota of the upper respiratory tract of man (PERERA ET AL) . Neisseria Meningitis can be classified into at least 13 distinct sero groups based on the antigenicity of the outer polysaccharide capsule (QUA GLIARELLO VINCENT ET AL,WENGER J D ET AL and). Although various meningococcal sero groups are responsible for sporadic cases of meningitis, major epidemics are caused primarily by group A (PATRICK S MOORE ,PATTERSON DAVID ET AL) and to lesser extent by group C meningococci. Neisseria meningitis is a common cause of meningitis of human's in that
2%-10% of healthy persons are nasopharyngeal carriers of potentially pathogenic meningococci. Spread is by person to person by airborne route. Respiratory transmission and meningococcal carriage rates do not necessarily correlate with the risk of invasive disease (QUA GLIARELLO VINCENT ET AL, SHELTON M M ET AL and WENGER J D ET AL). Since the late 1940's to date, group A Meningococcal epidemics have been rare in industrialized nations, in contrast, intense meningococcal epidemics have been reported in a number of developing countries including Brazil, Nepal, China, Sub-Saharan African Nations. Zambia lies in broad savanna region of Africa extending from Gambia to Ethiopia, Kenya, Tanzania and Zambia known as the meningitis belt (ref 6,16). This region is uniquely susceptible

to intense group A Meningococcal epidemics that occur in 8 to 14 year cycles.

Rates of diseases are seasonally dependent peaking during the dry cold season and declining rapidly with the onset of rains, similar epidemics occur in China.

Seasonal variation and presentation pattern of these epidemics in Africa result from a complex interaction between the host, the organism and the environment (QUA GLIARELLO VINCENT ET AL,WENGER J D ET AL).

Host factors that have been known to predispose to Meningococcal Meningitis include:- (a) Humoral Immunity (WENGER J D ET AL), (b) Nutritional status, (c) Presence of respiratory tract infection. Studies have shown that the risk of meningococcal disease is inversely related to a patient's pre-existing bacteriocidal antibody titres
against the causative sero-group. In support of this is the observation that, meningococcal attack rates in the United States are highest for children 9 - 12 (WENGER J D ET AL) months, the age at which maternally derived antibodies are lost.

There is also evidence of Natural Immunity which results from infection with non Pathogenic Neisseria Lactemica which stimulates formation of cross protective antibodies, which in turn appear to be protective during the critical period between infection and development of specific immune response against a pathogenic meningococcal strain (WENGER J D ET AL).

Loss of Herd Immunity against group A meningococcus has been implicated as possible explanation of the epidemic cycles in the Sub-Saharan Africa (PATRICK S MOORE) (b) Respiratory tract infections increase susceptibility to meningococcal disease through damage of pharyngeal mucosa.

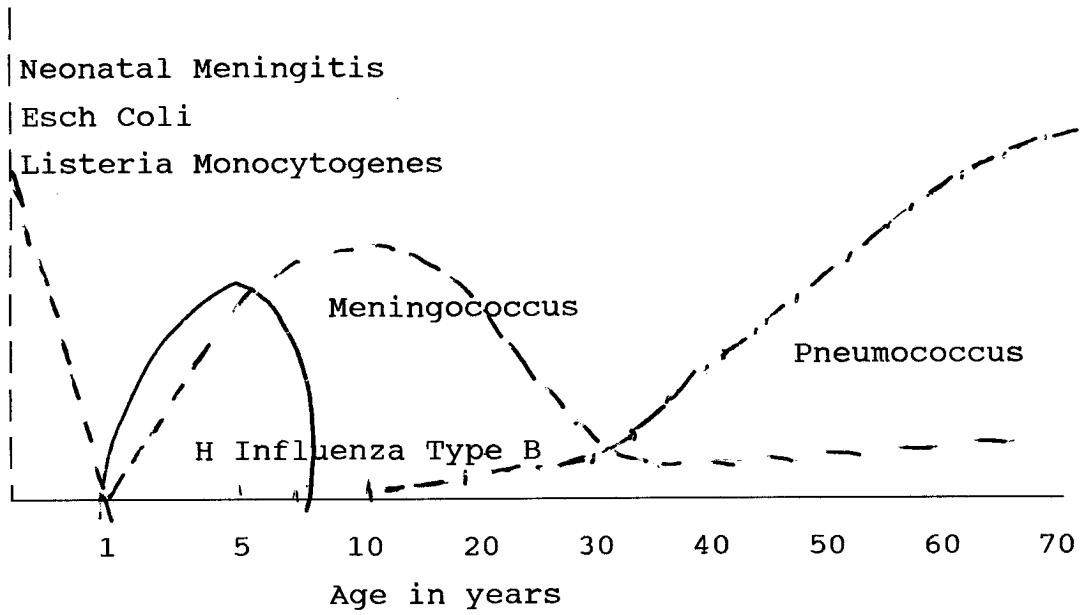
The organism (i) variation in virulence between strains of Neisseria Meningitis may contribute to an epidemic. (ii) Different strains within the sero group A. (iii) Antigenic variation between Neisseria Meningitis group A. clones can be responsible for sudden loss of Herd Immunity.
Environment: (QUA GLIARELLO VINCENT ET AL ,PATRICK S MOORE). Appropriate environmental condition e.g. Dry
season, with low humidity plus high temperature increase invasiveness of meningococci. These environmental factors enhance successful meningococcal invasion by damaging the mucosal barrier.

UPPER respiratory infections contribute to the seasonality of meningococcal meningitis in Africa , in that both respiratory tract infections and otitis media occur most frequently during the dry season in Africa.

Whereas the commonest cause of bacterial meningitis in both children and young adults is neisseria meningitides, when there is a meningitis epidemic, haemophilus influenzae type b and the pneumococcus bacteria may also be responsible for a significant number of cases of meningitis However although the three main bacterial species may cause meningitis in any age group, the incidence of the different types varies with age. In infants beyond the neonatal period and young children up to the age of 5 years H. influenza type b and meningococcus are both common causes of infection, over the age of 5 years Haemophilus meningitis is rare and throughout the remainder of childhood and into adult life , meningococcus is the predominant cause of bacterial meningitis. Primary pneumococcal meningitis is rare in children or young to middle aged adults but becomes increasingly common with advancing age and is the commonest form in the elderly. (ROOS K L ,BI DUERDEN ET AL,PATTERSON DAVID K ET AL)

figure 1

Age group incidence of the major types of Bacterial meningitis. From: A new short textbook of Microbial and parasitic infection by BI Duerden; TMS Reid; JM Jewsbury and DC Turk.



Also important in the etiology of meningitis are staphylococcus aureus and staph epidermidis. Staph epidermidis accounts for 75& of infections associated with shunting procedures for hydrocephalus , and staph Aureus occurs largely in post-operative neuro-surgical patients, in patients with vertebral infection and as a complication of S.Aureus endocarditis.Other rarer causative organisms include Group B Streptococci and gram negative bacilli usually in association with brain abscess, epidural abscess,head trauma,neuro-surgical procedures or cranial thrombophlebitis. Escherichia coli, Klebsiella, Enterobacter, Proteus, Citrobacter , Pseudomonas, and Acinetobacter calcacetian, usually as a consequence of head trauma, neuro-surgical procedures, spinal anaesthesia, lumber puncture,or shunting procedures. Gram negative bacilli may cause meningitis in neonates, elderly persons above the age of 50 years and in adults with debilitating diseases.Rare meningeal pathogens include, Salmonella, Shigella, Clostridium perfringens and Neisseria gonorrhoea. Listeria monocytogenes is becoming an important cause of meningitis in infants , the elderly and adults

with immunosuppression, secondary to transplantation, cancer chemotherapy and connective tissue diseases.(PATTERSON DAVID K ET AL,QUA GLIARELLO VINCENT ET AL,TUOMANEN E ET AL)

1.3.PATHOLOGY

The effect of bacteria or other organisms in the subarachnoid space is to cause an inflammatory reaction in the pia and arachnoid and in the cerebrospinal fluid .In pyogenic meningitis pus accumulates in this space. If the natural history is not interrupted, the infective agent or its toxin, injures those structures which lie within the subarachnoid space, or ventricles and adjacent to it. The purulent material may block the flow of CSF. resulting in obstructive hydrocephalus. (PATTERSON DAVID K ET AL,QUA GLIARELLO VINCENT ET AL,TUOMANEN E ET AL)

1.4 PATHOGENESIS

Bacterial meningitis ensues when pathogenic vilurent factors overcome host defence mechanisms. In this regard , the neurotropic potential of the most common bacterial causes of meningitis S Pneumoniae, Haemophilus influenzae, Neisseria meningitides and Escherichia coli , relates to their ability to evade several host defences,specifically ,the successful meningeal pathogen must sequentially colonize host mucosal epithelium,invade and survive in the intravascular space, cross the blood brain barrier survive in the CSF. The 3 most common meningeal pathogens are invasive and depend upon antiphagocytic capsular surface antigens for survival in the tissues of the infected host. All express their pathogenicity largely in the form of extracellular proliferation. All three are inhabitants of the Nasopharynx. Factors which predispose the colonized patient to bloodstream invasion include,

1. Antecedent viral infections of the upper respiratory passages;
2. In the case of pneumococcus, infection in the lung and the absence of bactericidal antibodies;
3. Deficiencies in the terminal components of complement in H. influenzae and meningococcal infection.

Once bloodborne, the factors that lead to meningeal localization of bacteria are unknown, but it has been postulated that the three common meningeal pathogens posses a unique predilection for the meninges. Bacterial entry into the subarachnoid space may be facilitated by disruption of the blood barrier by trauma, circulating endotoxin, inflammatory cytokines or an initial viral infection of the meninges. Once CSF entry occurs bacterial replication proceeds readily because levels of immunoglobulin and complement are too low to permit opsonization and or bacterialysis and phagocytosis by neutrophils.(PATTERSON DAVID K ET AL,QUA GLIARELLO VINCENT ET AL.TUOMANEN E ET AL)

Bacteria can also gain entry to the meninges through congenital neuroectodermal defects, craniotomy sites, diseases of the middle ear and paranasal sinuses and cranial trauma notably skull fractures.Once developed characteristic features of bacterial meningitis include an increase in intracranial pressure, disruption of the blood brain barrier, cerebral oedema and alterations in cerebral blood flow. (PATTERSON DAVID K ET AL,QUA GLIARELLO VINCENT ET AL,TUOMANEN E ET AL)

1.5 PATHOPHYSIOLOGY

Clinical Meningitis arises largely from the host response to the inciting organisms in the CSF.(PATTERSON DAVID K ET AL,QUA GLIARELLO VINCENT ET AL,TUOMANEN E ET AL)

BACTERIAL VIRULENCE FACTORS:

It has been observed that the cell wall and lipopoly-saccharides of bacteria are more important determinants of meningeal inflammation and breakdown of the blood brain barrier than the bacterial surface components involved in CSF invasion.(PATTERSON DAVID K ET AL,QUA GLIARELLO VINCENT ET AL,TUOMANEN E ET AL)

BREAKDOWN OF THE BLOOD BRAIN BARRIER:

The cerebral microvascular endothelium is the primary site of the breakdown of the blood brain barrier; normally the endothelium has unique ultrastructural properties specifically rare plasmalemma vesicles and continuous intercellular tight junctions that enable it to function as a high resistance endothelium and serve as a barrier to circulating macro molecules e.g. albumin.(PATTERSON DAVID K ET AL,QUA GLIARELLO VINCENT ET AL,SHELTON M M ET AL.)

When infection occurs there is an increase in cytoplasmic plasmalemma vesicles and complete separation of the intercellular tight junctions in the micro vessels which correlate with the exit of albumin into the CSF.(SHELTON M M ET AL,QUA GLIARELLO VINCENT ET AL)

Studies have shown that within one to three hours of inoculation of bacterial products into CSF there is a brisk release of TNF interleukin-1 and interleukin-6 into the CSF that proceeds inflammation or the exudation of protein and there is evidence that these cytokines are responsible for the injury and breakdown of the blood brain barrier(PATTERSON DAVID K ET AL,QUA GLIARELLO VINCENT ET AL,TUOMANEN E ET AL).

Intracranial pressure often increases in patients with bacterial meningitis and it results from

(a) Brain oedema which may be vasogenic caused by increased permeability of the Blood Brain Barrier or
(b) Cytotoxicity caused by toxins released by bacterial or neutrophils or interstitia caused by CSF outflow resistance.(SHELTON M M ET AL,QUA GLIARELLO VINCENT ET AL)

Meningitis also results in alterations in cerebral blood flow initially the flow increases but as intracranial pressure rises and CSF lactate concentration increases the flow drops. These delays in blood flow are related to the loss of cerebrovascular autoregulation such that cerebral blood flow fluctuates directly with the mean arterial blood pressure.(PATTERSON DAVID K ET AL,QUA GLIARELLO VINCENT ET AL,TUOMANEN M ET AL)

1.6 SYMPTOMATOLOGY:

Fever, headache, photophobia, seizures, vomiting, impairment of consciousness, stiff neck and backache are common to bacterial meningitis irrespective of its aetiology.(ENAO D ET AL, QUA GLIARELLO VINCENT ET AL and SHELTON M M ET AL).

In about 25% of patients, the onset is fulminant and patients become seriously ill within 24 hours.In over 50% meningitis develops over 1 - 7 days and is associated with respiratory symptoms.(ENAO D ET AL,QUA GLIARELLO VINCENT ET AL,SHELTON M M ET AL)
The classical symptoms of meningitis may be minimal in elderly, and debilitated patients in whom low grade fever and changes in mental state may occur without headache or nuchal rigidity(SHELTON M M ET AL).
Meningococcal meningitis correlates with special clinical features such as:

(a) Rapid evolution
(b) Morbilliform, petechial, or purpuric skin eruptions(QUA GLIARELLO VINCENT ET AL,SHELTON M M ET AL,TUOMANEN E ET AL)
(c) Larger ecchymoses and lividity of skin in the lower part of the body (d) Circulatory collapse.(SHELTON M M ET AL)

Pneumococcal meningitis is usually preceded by an infection in the lungs ears and sinuses. (PATTERSON DAVID K ET AL,QUA GLIARELLO VINCENT ET AL,TUOMANEN E ET AL WEISS W ET AL)
Signs of focal cerebral disease are frequent in pneumococcal and H influenza meningitis and are probably the result of vasculitis and occlusion of cerebral veins with infection of cerebral tissue or they may be indicative of localized sites. Cranial nerve palsies are particularly frequent with pneumococcal meningitis.(QUA GLIARELLO VINCENT ET AL, SHELTON M M ET AL).

1.7 **LABORATORY FINDINGS:**

(a) The number of leukocytes in CSF averages between 5,000 and 20,000 per milliliter. Neutrophilic leukocytes.

(b) Pressure is consistently elevated above 180 mm of water.

(c) Protein levels of CSF are higher than 45 mg/dl

(d) Sugar concentration in CSF is depressed to less than 40mg/dl

(e) Gram stain of sedimented CSF will permit identification of the organism.

(f) CSF culture is positive in 70 to 80% of cases

(g) Blood cultures are positive in 40 to 60% patients

(h) Blood leukocyte count is generally elevated with a shift to the left.

OTHER TESTS.

X-rays of chest, skull and sinuses may provide clues.

1.8 **COMPLICATIONS OF BACTERIAL MENINGITIS:**

The longer the duration the greater the chances of complications such as:

(a) Cranial nerve palsies involving 3rd, 6th, 7th and 8th cranial nerves occur in 10 to 20% of cases and usually disappear within a few weeks.

(b) Deafness especially with pneumococcal, H-influenza + meningococcal infections.

(c) Focal lateralizing neurological signs are usually indicative of vasculitis and cerebral infarcts

(d) Retardation and epilepsy

(e) Coma

(f) Brain abscess

(g) Subdural empyema

1.9 **DIFFERENTIAL DIAGNOSIS:**

1. Viral Meningo Encephalitis
2. Tuberculous Meningitis
3. Leptospiral Meningitis
4. Fungal Meningitis
5. Behcets Syndrome
6. Mollaret's Meningitis

1.10 **PROGNOSIS:**

Worsened by old age, infancy, abrupt onset, bacteremia, coma, seizures, diabetes mellitus and head trauma.

1.11 **TREATMENT:**

Bactericidal drugs recommended:-

Penicillin G 18 to 24 million units Intravenously in 4 to 6 divided doses.

H Influenza - Ampicillin + Chloramphenicol.
Chloramphenicol 4 to 6 g per day
Third generation Cephalosporins
Antibiotics to be given for ten days
Prevention - Polycysaccharide Antigens of organisms of serogroup A + C - Group specific antibodies.

1.12 COINFECTION WITH HUMAN IMMUNODEFICIENCY VIRUS (HIV):

Coinfection with HIV has been reported to be a significant factor in African outbreaks of meningitis because of the high seroprevalence of HIV in some African cities (PATRICK S MOORE PATTERSON DAVID K ET AL). Even though AIDS has been reported through out the world, it has been found to be particularly prevalent in Central Africa, where sero-epidemiological studies have shown that infection with HIV or a closely related virus is endemic and is spread by heterosexual intercourse causing mild disease (GUISEPPE PANTALEO ET AL).

The acquired immunodeficiency syndrome was originally defined by the centers for Disease Control as the presence of a reliably diagnosed opportunistic disease that is indicative of an underlying defect in cell medicated immunity in the absence of known causes of underlying immune defects such as iatrogenic immunosuppression or malignant neoplasms. (GUISEPPE PANTALEO ET AL). AIDS is caused by HIV, a human retrovirus of the lentivirus group: The Human Immunodeficiency Viruses are two, namely HIV-1 and HIV-2. Both of which are cytopathic viruses. The commonest cause of AIDS through out the world is HIV-1. HIV-2 has about 40 percent sequence homology with HIV-1 and is more closely related to some members of a group of simian immunodeficiency viruses, and has been identified predominantly in Western African countries. HIV is an RNA Virus and has the retroviral genes env, gag and pol and six extra genes involved in the replication and other biologic activities of the virus.(GUISEPPE PANTALAO ET AL)

1.13 INCIDENCE AND PREVALENCE:

The first cases of Acquired Immunodeficiency Syndrome (AIDS) were recognised in the United States in 1981 and the causative virus was identified in 1983,by Barre-Sinouss et al. The first case of AIDS caused by HIV 1 in Zambia was reported in 1984 and by March 1992 the Ministry of Health and the National AIDS Prevention Programme indicated that the total cumulative AIDS cases had shot up to 5,843 while the total cumulative ARC cases was 18,676 (GAISIE KWESI, WHO UNPUBLISHED DATA)

The major mode of transmission of HIV in Zambia is through heterosexual contact. Infected mothers may transmit the virus to infants perinatally. Virus can also be transmitted from the mother to the infant via breast feeding.(ENAO D ET AL,GAISIE KWESI) HIV1 is the major virus causing AIDS in this country.

The Immunodeficiency state is predominantly of cell-mediated immunity type, and results from attachment of the virus to CD4 receptor molecules, present on the surface of T4 lymphocytes, monocytes, histiocytes, follicular dendritic cells, langerhans) and brain cells including both neurons and glial cells. Binding of gp 120 to CD4 leads to fusion of viral envelope and cell membrane and direct contact of virion contents and host cell cytoplasm. A cell already infected and expressing gp120 on its surface may bind to and fuse with multiple uninfected DC4+ cells to form syncytia, which later die.

The pathogenic mechanisms associated with HIV infection include:- (a) Functional abnormality and quantitative defection of CD4 Tlymphocytes (b) Single-cell killing and cyncytia formation occur through direct HIV - mediated cytopathic effects.Progressive destruction of the cells results in impaired cell mediated immunity which predisposes the patients to the risk of developing life threatening opportunistic infections with one or more pathogens.(GUISEPPE PANTALEO,ENAO D ET AL,GAISIE KWESI)

The full blown clinical presentation of AIDS is the final outcome of the progressive deterioration of the immune system which presents with severe and persistent constitutional signs and symptoms, opportunistic infections and neoplasms.

The clinical consequences of HIV infection form a spectrum ranging from the Asymptomatic state to severe disease. Severe immunosuppression is associated with conditions like oral and oesophageal candidiasis which may also involve the nasopharyngeal mucosa,a process that may result in erosion of the mucosa and interfere with the production of secretory IgA, both conditions that may facilitate infection with pathogenic organisms which normally inhabit the oropharynx including opportunistic organisms Such as candida itself, and may therefore predispose these individuals to meningitis (ENAO D ET AL,GAISIE KWESI,BI DUERDEN ET AL).

It has also been found that some major histocompatibility - complex (MHC) class II molecules particularly HLA-DR and HLA-DQ share some degree of structural homology with the gp120 and gp4 proteins of HIV type 1 and antibodies to these HIV proteins therefore cross react with HLA class molecules and interfere with the functions of cellular interaction of antigen presenting cells and inhibit antigen specific functions mediated by Helper CD4 T cells. Autoimmune mechanisms have also been associated with depletion of complement, a situation that may predispose these patients to sustained bacteremia further predisposing these patients to meningitis. Confection of meningitis and HIV infection may thus be perceived as a serious medical emergency which requires emergency attention of all medical personnel.

2.0 STATEMENT OF THE PROBLEM

Zambia lies at the Southern border of the meningitis belt of Sub-Saharan Africa and this region is endemic for sero Group A meningococcal Meningitis. Therefore geographically cyclical

epidemics of meningococcal meningitis are expected. However despite the fact that epidemics have occurred in this part of the world since 1880s, and despite the introduction of new antimicrobials, the morbidity and mortality associated with meningococcal disease remain very high.

The last wave of the epidemic which began in the late 80s with peaks in 1991, 1992 and 1993 presented with features that had not been noted before, whereas individuals living in endemic regions are supposed to develop some immunity to meningococcal disease, and epidemics occur when this herd immunity drops, with attack rates being higher in the very young, the last epidemic saw no such characteristics; many patients came in, the young, the middle aged and the old. Most of the patients came in very sick, many with meningocaemia and most of them died in the admission ward either before they received medical help or during the process of being helped.(University Teaching Hospital medical records.)

In other words, most of these patients were presenting with fulminant disease, evidently something had happened to change the clinical presentation of this disease in this environment.
Figures from UTH showed that out of a total number of 32,012 admissions to the medical wards for 1991, 5376 (16 per cent) were due to meningitis. Of the 5376 admissions 2470 were discharged but 2900 (54 per cent) died (UTH medical records 1991). Giving a case fatality rate of 54 per cent for meningitis. This case fatality rate is very much higher than the acceptable expected case fatality rates for this disease which is between 5% and 15%.
Fulminant disease is usually associated with

(a) Change in virulence of the organism.
(b) Host factors that affect the hosts immunity eg.
    (i) Old age and infancy(ENAO D ET AL,GAISIE KWESI,BI DUERDEN ET AL)
    (ii) Alcoholism and hemosiderosis which interfere with normal hepatic clearance of IgA (SHELTON M M ET AL)

(iii) Biliary tract disease and haemoglobino-pathies which also interfere with clearance of IgA.

(iv) Systemic diseases such as Diabetes Mellitus, Multiple Myeloma, Systemic Lupus, Erythromatosis Hepatic Failure and Nephrotic Syndrome which are associated with secondary complement deficiency or depletion of (C1, C3 or C4).(QUA GLIARELLO VINCENT ET AL,SHELTON M M ET AL)

Looking at the clinical presentation of the patients in UTH, most of them did not have the above mentioned diseases that are associated with impairment of the Host's immunity. The only other condition that was in epidemic proportion was HIV in infection, however, since no data was available to show whether the incidence and presentation of meningitis had changed since the beginning of the HIV/AIDS epidemic, or not, the association between the two epidemics was an area open to research.

The country, had two epidemics affecting its population, however, there was still no documentation to show whether the presentation of meningitis had changed since the beginning of the HIV/AIDS epidemic. In an effort to find if there was any relationship at all between the two epidemics, the author looked closely at data that had been collected in the UTH for the purpose of finding the HIV load in in-patients. This survey had been done for a period of 5 days beginning 31st August, 1992 to 4th September, 1992 whereby all in-patients and all those that were admitted during that week were screened anonymously for their serostatus. A total number of 419 patients were screened in that week, in Phase V Medical Admission Ward, and amongst these, there were 25 cases of meningitis. Of the 419 patients data of 58 patients was discarded as the forms were incomplete, therefore, data of 361 patients was analysed. The serostatus of these 361 patients was as follows: 257 HIV positive and 104 HIV negative giving an overall seropositivity rate of 71%.

The serostatus of the patients with meningitis was as follows: 15 HIV negative and 10 HIV positive giving a seropositivity rate

among the meningitis cases of 40%.

Given that HIV infection causes progressive deterioration of the immune system via:-

(a) Qualitative as well as functional defects in CD4 T cells. (QUA GLIARELLO VINCENT ET AL,SHELTON VINCENT ET AL)

(b) Autoimmune mechanisms due to the fact that Nonpolymorphic determinants of major-histocompatibility complex class II Molecules, particularly HLA-DR and HLA-DQ, share some degree of structural homology with the gp.120 and gp41 proteins of HIV type 1, and antibodies to these HIV proteins could, therefore, cross react with HLA Class II molecules.(GUISEPPE PANTALEO,ENG R H ET AL)

(c) The Lymph nodes in patients with HIV infection have been confirmed to act as reservoirs of HIV infection whereby HIV particles in complex with antibodies and complement accumulate in lymph nodes where they are trapped within network of follicular dendritic cells in the germinal centers. (GUISEPPE PANTALEO)

All these mechanisms may be associated with depletion of complement system components as previously shown with other systemic diseases that predispose a patient to have fulminant meningitis.As well as this, HIV infection is associated with impaired cell mediated immunity which would predispose these patients to Respiratory infections,and bacteremia with encapsulated organisms all of which are known to be risk factors of meningitis.

Given the above High Case fatality rate of meningitis and a possible relationship with the AIDS epidemic the author was compelled to look at this possible relationship closely.

RATIONAL OF THE STUDY:

Even though meningitis has been with us for many years, and we have had epidemics of meningococcal meningitis in the past, because of Zambia's location in the African Meningitis Belt, little work has been done to find out whether the face of meningitis has changed in the recent years as a result of the

HIV/AIDS epidemic. This will probably be one of the first few studies in Zambia to determine whether the presence of the HIV/AIDS epidemic has an effect on the presentation of Bacterial Meningitis.

Information obtained from this study will benefit:-
The Zambian Nation as a whole in that the information obtained will be used by planners of Health Services delivery at the Ministry of Health, Physicians who take care of meningitis patients to understand some of the bizarre presentations of meningitis that we have recently observed, students and researchers involved in research work on HIV/AIDS and meningitis and lastly but not the least the patients that we take care of.

2.01 OBJECTIVES OF THE STUDY:

The major objectives of the research project were as follows:-

(1) To determine the prevalence, clinical and epidemiological features of meningitis in the presence of a Human Immunodeficiency Viral Infection Epidemic,

(2) To establish whether there is a significant relationship between meningitis and Human Immunodeficiency Viral Infection, (3) To establish the common organisms causing the current meningitis epidemic,

(4) To determine whether the management of meningitis should be modified in a patient with HIV infection and

(5) To determine whether patients who have both meningitis and HIV infection develop more complications and whether or not their outcome is different from that of patients who do not have HIV infection.

2.0.2 HYPOTHESIS OF THE STUDY:

1. Meningitis has a fulminant presentation, greater complications and greater mortality in patients with HIV infections as compared to those who do not have HIV infection.

2.0.3 REVIEW OF RELEVANT LITERATURE

Literature in Zambia on AIDS and Meningitis is lacking. However many studies have been done elsewhere which point to the fact that the presentation of meningitis has changed in many ways as a result of the AIDS epidemic e.g. (1) The organisms causing meningitis. (2) Clinical presentation. Opportunistic organisms that previously rarely caused meningitis are now being found e.g. Cryptococcal Meningitis (WENGER J D ET AL,SHELTON M M ET AL,WEISS W ETAL,ENG RH ET AL & TUOMANEN E ET AL), Salmonella Meningitis (BI DUERDEN ET AL), Listeria Monocytogens, Tuberculous Meningitis (BI DUERDEN ET AL and WILSON BRAUNWALD),
Toxoplasmosis ,Pneumococcal , Lancefield Group B, Stretococcus

Meningococcal disease has been reported in a patient with AIDS and disseminated disease due to encapsulated bacteria occurs more frequently in persons infected with HIV (RAVIGLIONE M C ET AL). The present AIDS epidemic in the East African Meningitis Belt could significantly change the behaviour of Group A Meningococcal epidemics in this region.

In a study by Redd S L et al, to show the role of HIV infections in pneumococcal bacteriaemia identified, the authors found that out 290 patients with bacteriaemia, 32 (11%) had AIDS at the time that the pneumococcal bacteriaemia was diagnosed and another 43 (15%) were HIV infected but did not have AIDS. The investigators reported that the rate of pneumococcal bacteriaemia was approximately 100 - fold greater in AIDS patients in San Francisco than rates reported before the AIDS epidemic. This is a significant finding more especially if we take into consideration the fact that primary meningitis usually results from bacteriaemia(MUSTAFA M M ET AL).

HIV infection also changes the clinical presentation of meningitis as evidenced by a Report of Shiantaky who reports a case of purulent mycobacteria meningitis in AIDS. Reports are also available on the evidence of drug resistance by organisms to antibiotics e.g. (ENG R H ET AL).

3.0. OPERATIONAL DEFINITION OF KEY TERMS:

(a) Meningitis - Defined as Inflammation of the Meninges of the Brain and Spinal Cord.

(b) Neck stiffness, resistance to dorsiflexion of the head caused by cervical and upper thoracic paraspinal muscle spasm secondary to meningeal inflammation.

(c) HIV - Human Immunodeficiency Virus, a retrovirus with an affinity for the T4 antigens on lymphocytes and other blood borne cells (including monocytes and macrophages).

4.0 PLACE OF STUDY

PLACE OF STUDY: UNIVERSITY TEACHING HOSPITAL (UTH) LUSAKA, ZAMBIA.

This study was carried out at the University Teaching Hospital in Lusaka. It is the largest Hospital in Lusaka as well as in Zambia. It serves a total population of one million in Lusaka urban as well as acting as the Tertiary Care facility for the rest of the country. The Hospital has a total bed capacity of 2000 beds and the total bed capacity of the Medical Wards is 400 beds with a high bed occupancy rate of over 120% due to floor beds.

Lusaka is the Capital city of the country and has a total population of one million which is 12% of the total population of Zambia.

Zambia is a land locked country in Central Africa, covering an area of 752614 square kilometres, consisting of about 2.5% of the area of Africa. It lies in the Southern Tropics between 8 and 18 degrees South latitude and between 20 and 35 degrees East longitude, with an average altitude of 1,127 metres above sea level.

It has a tropical climate and the vegetation is savanna woodland and there are three (3) distinct seasons, warm - wet season stretching from November through April, a cold dry season from May to August with a minimum temperature of varying between 14 and 30 degrees centigrade and hot dry season from late August to October.

Zambia has a mixed economy consisting of modern and urban oriented sector confined to the line of rail and Rural agricultural sector.(BULLETIN OF HEALTH STATISTICS 1987-1988,GAISIE KWESI)
Copper mining is the country's main economic activity, accounting for 95% export earnings and contributing 45% government revenue. Other important minerals mined are Cobalt, Coal, Zinc, Lead and

Manganese.

The Gross National Product for the country in 1985 was 2593 million US Dollars with a GNP per capita of US$390. These figures have since fallen due to economic recession which has affected the country in the last eight to ten years. In an effort to combat the economic recession the country has passed through the Structural Adjustment Programme to what is now known as the Economic Recovery Programme. These programmes have affected the provision of social services such as Health and Education negatively. The standard of living has dropped for the under privileged resulting in a rise of infectious diseases like T.B, Diarrhoeal diseases and Malnutrition. The introduction of cost sharing in Health services has further complicated the picture in that most people wait until they are very sick before they come for treatment in Health Care Institutions, a trend that may produce adverse outcomes in diseases like Meningitis and pneumonia whose prognosis depends on how early or late in the disease process that effective antibiotic interventions commenced.

The 1969, 1980 and 1990 national censuses reported total population of 4.0 million, 5.7 million and 7.8 million respectively, implying growth rates of 3.1 and 3.2 percent per annum between 1969 - 1980 and 1980 - 1990 respectively (Demographic and Health Survey 1992). The population density increased from 5.3 people per square kilometre in 1969 to 7.5 in 1980 and 10.4 in 1990. Urbanisation has steadily increased from 29% in 1969 to 42 in 1990.(BULLETIN OF HEALTH STATISTICS, 1987 - 1988,GAISIE KWESI)

The average life expectancy at birth climbed from 43 years in 1969 to 51 years in 1980 and had risen to 54 years by 1990. On an average the Zambian woman lives two to three (2 to 3) years longer than men. (Central statistical office 1990 a). It is important to note that 46.8% of the Zambia population is under 15 years of age (Census Data Central statistical office, 1985 b).

The government provides 3/4 of Health services with the remaining 1/4 being provided by the Mines, Mission Hospitals and the private sector. In 1982, the country had 81 Hospitals with a total number of 15,075 beds and cots. 779 Health centres and clinics providing a total of 5,860 beds and cots.

Note that the University teaching Hospital has a total Bed capacity of 2,000 beds which works out to be 2,000 out 15,075 of the total Country Hospital beds which is about 13%. The medical wards have in total bed capacity of 400 beds.

Total number of admissions to the medical wards for 1991 were 32,012 and these 5376 (16%) were due to meningitis. Of the 5376 admissions, 2470 were discharged but 2900 died giving a high fatality rate of 54% for Meningitis. whereas, meningitis is the 11th major cause of morbidity in UTH, it is the 7th commonest cause of death. The ten commonest causes of admission to the medical wards in 1991 were:-

(1) Falciparum Malaria
(2) Pneumonia
(3) Gastroenteritis and Colitis
(4) Pulmonary tuberculosis
(5) Bacillary Dysentery
(6) Miscellaneous III-Defined
(7) Protein Calorie Malnutrition
(8) Hypertensive Disease
(9) Acute Upper Respiratory Infection
(10) Anaemia
(11) Meningitis
(Source UTH Medical Records)

With the coming of the HIV epidemic in the early 1980's the profile of the patients on the medical wards changed in many ways, whereas, previously the wards were full of elderly patients who came in for treatment of chronic medical conditions such as Diabetes Mellitus, Hypertension, strokes and heart diseases, the patients were now much younger, a lot sicker coming in with

various infectious diseases and not responding favourably despite intense medical intervention. Patients coming in with symptoms

of meningitis were equally coming in with bizarre presentation, some with complications that the medical personnel could not deal with.

Having identified the high fatality rate associated with meningitis and having recorded high HIV positive seroprevalance rate in patients admitted to the medical wards in the University Teaching Hospital (UTH unpublished Data 1992), it became obvious that there was need to study the relationship between meningitis and HIV infection in this environment.

4.1 STUDY POPULATION:

The study population consisted of all adult patients (18 years and above) admitted to Phase V admission ward with a clinical diagnosis of meningitis, during the study period.

4.2 INCLUSION CRITERIA:

Clinical presentation determine inclusion into the study were as follows:

(a) Acute febrile illness
(b) Headache
(c) Neck stiffness
(d) Positive Kernigs
(e) A turbid CSF
(f) Change in mental status.

4.3 EXCLUSION CRITERIA:

Patients presenting with the above clinical presentation but whose laboratory findings confirmed a diagnosis of severe/cerebral malaria, viral meningitis, patients with Kaposi Sarcoma, Lymphoma, patients with neurological deficits e.g. hemiplegia,

which the patient may have had before the onset of the current attack of meningitis. Patients who refused to have the HIV test and also patients who refused to participate in the study. Patients who were too ill to give their consent were included in the study if the relatives gave consent.

5.0 METHODOLOGY

A combination of Research designs was used namely, descriptive and comparative research designs.

DESCRIPTIVE research methods were used to

(1) Establish demographic characteristics of the population under study.
(2) Establish the types of meningitis in the study population.
(3) To describe the clinical presentation and progression of the meningitis.

Given that at the time of recruitment the HIV sero status was not known and it took time before the serum results were known to the researcher, a retrospective comparative research design had to be used to compare the two groups i.e the group that turned out to be HIV positive compared with the group that turned out to be HIV negative. The dependent variable was outcome of meningitis and the independent variables screened were:-

1. HIV Serology
2. Sex
3. Age
4. Nationality
5. Religion
6. Residential area whether high or low
7. Number of persons in the current home
8. Marital status
9. Extra marital sexual activities
10. Social habits
11. Education completed
12. Occupancy
13. History of exposure to meningitis
14. Duration of symptoms
15. Evidence of immunosuppression

5.1 THE RESEARCH INSTRUMENTS

The questionnaire had 5 sections and nine parts.
Questions one to ten (1 to 10) were designed to establish demographic characteristics of the study population.
Questions 11 to 15 were designed to asses possible risk practices associated with HIV infection.

Questions 17 to 21 aimed at establishing risk factors predisposing a patient to meningitis.
Questions 22 to 23 were designed to find out the duration of symptoms before patients sought medical care.
Questions 34 to 44 were designed to collect information on the clinical presentation of the patients.
Questions 45 to 50 were used to assess physical signs that have een found to be associated with HIV infection in other studies.
Question 51 to 56 dealt with laboratory data.
Question 57 recorded the medications given
Question 58 was designed to collect information on clinical progression.

Data for this study was collected over a period of four months from 1st December 1993 to end of March 1994. Most of the patients were recruited in the admission ward. The investigator working in conjunction with the doctors in the admission ward was informed of all cases that presented with symptoms and signs of meningitis. The investigator then introduced herself to the patient or close relatives of the patient if the patient was too sick and informed them of the meningitis study what the major objectives of the study were and the purpose of the study. The investigator also informed them that a number of investigations would be done including the HIV test and that the results would be kept confidential and would only be used for the purpose of this study. The HIV test was explained to the patient, as to what it is, in that the test detects antibodies to the Human Immune Deficiency Virus, and that the presence of antibodies only showed that the patient had been in contact with the virus at some point but that this test does not tell exactly when this infection occurred and neither does it tell whether or not an individual would progress to develop AIDS.

If the patient and or relatives were agreeable they signed a consent form, and the investigator then went ahead to recruit the patient. The investigator, took a complete medical and social history, performed a complete medical physical examination, then

collected blood for full blood count, urea and electrolytes, blood culture and blood for HIV test. A lumbar puncture was then done, the pressure checked and CSF obtained examined for appearance and then sent to the laboratory for glucose, protein, cell count grams stain, nigrosin stain, culture and sensitivity. The patient was then commenced on treatment. The investigator then followed the patient up everyday to monitor the clinical progression of the meningitis, until the patient was discharged from hospital. Those patients that did not want the HIV test done, were not recruited and if on physical examination any of the exclusion criteria were identified, the patient was not included in the study. A questionnaire was then completed for each patient recruited.

5.2 METHOD OF DATA COLLECTION:

1. The questionnaire was designed to record:
   (a) Informed consent
   (b) Demographic data of their patient
   (c) Clinical examination findings — History; Physical examination; Fundoscopy
   (d) Lumbar puncture cerebral spinal fluid results
      - appearance
      - pressure
      - cytological
      - biochemical
      - microbiological
   (e) Blood was drawn and sent for:-
      - full blood count
      - urea and electrolytes
      - liver function tests
      - blood cultures
      - HIV test
   (f) Urine analysis
   (g) Chest X-ray
   (h) A record was kept of all the medications that the patient received during the course of the study

6.0 ANALYSIS OF DATA

During the four months study period beginning 1st December 1993 until 31st March 1994, a total number of 421 confirmed cases of meningitis were admitted to the University Teaching Hospital. 256 adults and 165 children. Of the 256 adults 81 died giving a fatality rate of 32.4% in adults and out of the 165 paediatric cases 63 died giving a fatality rate of 38%. (UTH Medical Records Statistics Dept).

TABLE 1.

UTH BOARD OF MANAGEMENT - MEDICAL RECORDS STATISTICS DEPARTMENT

M E N I N G I T I S C A S E S - 1ST DEC 1993 to 31ST MARCH 1994

	D I S C H A R G E S			D E A T H S		
Months	Adults	Children	Total	Adults	Children	Total
1993 Dec	38	34	72	26	16	42
1994 Jan	39	24	63	25	10	35
1994 Feb	57	20	77	20	13	33
1994 Mar	41	24	65	10	24	34
GRAND TOTALS	175	102	277	81	63	144

6.1 RESULTS:

Out of the 256 adult cases of meningitis. A total number of 75 patients, 30 females and 45 males agreed to be interviewed and participate in the study and agreed to take the HIV test even though the majority 60 patients out of 75 (80%) were not interested in knowing the results. All of the 75 patients were diagnosed to have meningitis on the basis of a history of headache, fever, neck stiffness, confirmed by physical examination. Lumbar puncture and CSF examination.

TABLE 2: NUMBER OF MALES AND FEMALES IN THE SAMPLE:

CATEGORY	NUMBER	PERCENTAGE
Males	45	60%
Females	30	40%
TOTAL:	75	100%

TABLE 3: AGE DISTRIBUTION OF PATIENTS WHO PARTICIPATED IN THE STUDY:

The age range was 14 years to 73 with a mean age of 27 years. 57% of the patients were aged below 40 years

AGE GROUP	NUMBER	PERCENTAGE
10-19	8	10.6%
20-29	19	25%
30-39	17	22.6%
40-49	9	12%
50-59	3	4%
60+	1	1%
UNKNOWN	18	24%
TOTAL:	75	100%

ETHNICITY: all the 75 patients were black African Zambians born and living in Zambia.

RELIGION: There was no significant relationship between religion and development of meningitis.

RESIDENTIAL AREA: However there was a significant relationship between living in a high density residential area and development of Meningitis, out of the 75 patients recruited only 7 came from Medium Density areas and the rest 68 (98%) of the patients came from high density areas. The largest number of patients came

from Chawama Compound (7), followed by George Compound (5) and Emmasdale (5).

TABLE 4: DISTRIBUTION OF MENINGITIS ACCORDING TO RESIDENTIAL AREA

RESIDENTIAL AREA	NO OF CASES	RESIDENTIAL AREA	NO OF CASES
Chawama	7	Libala	1
George	5	Chilenje	1
Emmasdale	5	Kamwala	1
Kanyama	2	Chisamba	1
Kafue	2	Mwembeshi	1
Kabwata	2	Chaisa	1
Garden	2	Lilanda	1
Kabwe Rural	1	Kuomboka	1
Kalundu	1	Mumbwa	1
Luangwa	1	Kalingalinga	1
Chongwe	1	Kaunda Square	1
Rhodes Park	1	Matero	1
Marrapodi	1	Makeni	1
Chelstone	1	Paradise	1
Avondale	1	Chibolya	1
Misisi	1		

The average number of rooms lived in by the study patients was 2.5 and the average number of persons per room was 3.

Meningitis is an Airborne disease and over crowding an important risk factor for its transmission.

Social habits did not show any significant trend with a patient's presentation with meningitis. Though the questions 11 to 15 were designed to assess risk practices associated with HIV infection. The responses received were not satisfactory. Three patients felt that asking them questions about extra marital affairs had no relationship with their reasons for admission to hospital i.e. Meningitis and would not volunteer any information, only 2

patients accepted having had sex with multiple partners.

Analysis of questions to establish exposure to meningitis prior to admission revealed that some patients had pneumonia two to three days before onset of Meningitis. This was especially so for those patients that had pneumococcal meningitis and those patients that had otitis media.

Only two patients had history of contact with a patient of meningococcal meningitis within the same house. One was a 15 year old girl whose 18 years old sister died from meningitis two days before this patient was brought in shock and also died.

The average duration of symptoms before seeking medical help was 2 days. The range of duration of symptoms was from 0 days to 5 days. Two patients who came in with severe disease had been well until that day of admission.

7.0 CLINICAL FINDINGS

The Table below shows results of the symptoms which these 75 patients with meningitis presented with. The commonest symptoms were:

Headache in 75/75 (100%)
neckache in 60/75 (80%)
chills in 40/75 (53%)
high fever in 60/75 (80%)
backache in 20/75 (26%)
confusion in 10/75 (13.4%)
delirium in 10/75 (13.4%)
seizures in 8/75 (10.6%)
nausea + vomiting in 5/75 (6.6%)
discharge from ears in 2/75 (2.6%)

Three patients came in comatose and never regained their consciousness. Four patients presented with purpuric rashes an ecchymoses on lower limbs and were diagnosed to have meningococcaemia. All four were HIV positive. Two recovered but two died.

PHYSICAL SIGNS AT PRESENTATION

THE COMMONEST PHYSICAL SIGNS FOUND IN THE 75 PATIENTS WERE AS FOLLOWS:

(1) Neck stiffness 75/75 = 100%

(2) Positive Kernigs Sign 65\75

(3) High temperature 60\75

(4) Delirium 30/75

(5) Confusion 20/75

(6) Petechial haemorrhages in 4 patients

(7) Arthritis in 2 patients with meningocaemia

(8) Focal neurological deficits - 6

(9) Hypotension-2

(10) Shock-2

(11) Comma-8

(12) Convulsions and loss of consciousness-7

(13) Uncontrollable epistaxis in 2 patients

Physical signs related to an underlying immunosuppression were also looked for, oral candidiasis was present in 20 patients. Generalized lymphadenopathy was detected in 14 patients nail changes were noted in 15 patients where they presented as longitudinal hyperpigmented lines. Herpes Zoster scars were present in 4 patients.

Table 5: Shows the commonest physical findings elicited in patients with meningitis.

SIGN	SEROSTATUS		
	HIV+VE	HIV-VE	UNKNOWN
Neck Stiffness	44	19	
High temperature	28	19	12
Positive Kernigs Sign	32	19	12
Arthritis	2	0	12
Focal Neurological Deficits	4	2	
Oral Candidiasis	20	0	
Lymphadenopathy	14	0	
Herpes Zoster Scar	4	0	
Nail changes	15	0	

Table 6.

COMPLICATIONS OF MENINGITIS NOTED WITHIN THE SEVEN DAYS OF ADMISSION AMONG HIV POSITIVE AND HIV NEGATIVE PATIENTS:

COMPLICATIONS	SEROSTATUS		
	HIV+VE	HIV-VE	TOTAL
Seizures	5	2	7
Coma	5	3	8
Cranial Nervepalsies	4	2	6
Deafness	2	0	2
Shock	2	0	2
Meningococcocaemia	4	0	4
Hyperpyrexia	2	0	2
Paraplegia	2	0	2
Hemiplegia	4	0	4
Arthritis	2		2
Epistaxis	2	1	3
Hypoglyceamia	2		2
Death	26	4	30

The major complication was death whereby 26 out of 30 patients equivalent to 86% of cases were HIV positive and 4 out of 30 were HIV negative. The next major complication was coma which occurred in 8 patients followed by seizure disorder. As noted in the table above there were many more serious complications amongst the HIV +ve meningitis patients than among the HIV negative patients. This is in keeping with hypothesis put forward in this study.

8.0 LABORATORY DATA

Lumbar puncture was performed on all 75 patients and the findings are as presented in Table 6.

The pressure was not measured due to non availability of manometers, however if pressure was noted to be increased during the procedure of lumbar puncture it was reported as being raised. However this is very unscientific as there are

other factors that may affect the force with the CFS drops e.g. how free the needle is in the subarachinoid space.

TABLE : 7
SUMMARY PRESENTATION OF CEREBRO-SPINAL FLUID MICROBIOLOGICAL EXAMINATION:

M F	DEC93	JAN94	FEB94	MAR94	TOTAL	SEROSTATUS HIV+	HIV-
Total number of patients 45 30 with meningitis recruited to study	30	7	17	21	75	48	27
Turbid CSF	23	6	15	15	59		
Clear CSF/ Traumatic	5	0	1	0	6		
POSITIVE CULTURES:							
Neisseria	3	1	1	4	9	5	
Strep Pneumonia	2			3	5		
Haem Infl	0				0		
Salmonella	0	0	1		1	1	
Strep Faecalis	0				0		
Staph Auerus	0				0		
Crytococcus N	6	0	4	4	14	14	

Summary presentation of CSF appearance and results of gram stain and nigrosin done on the CSF.

A total number of 75 lumbar punctures were done and 65 reports (86%) were received and analysed. There were 59 out of 65 . Turbid specimens, 3 clear specimens and 3 traumatic specimens.

In the 4 months study period out of the 65 CSF specimens sent 15 out 65 23% showed positive cultures and the following organisms

were identified;

9 Neisseria Meningitides

5 Streptococcus pneumonia

1 Salmonella Species

All 65 CSF specimens were subjected to the Nigrosin stain for cryptococcal meningitis and 14 out of 65 (20%) were positive for cryptococcus Neoformans, and all the 14 cases of cryptococcus neofomans occurred in HIV positive patients.

The one case of Salmonella was also in a patient who was HIV positive. There was no difference in the incidence of Neisseria meningitides in the two groups in that 5 cases occurred in HIV +ve patients and 4 in HIV -ve patients.

Biochemical tests were also asked for to be done on the CSF namely protein and sugar levels. However during the months of December 1993 until mid February 19940 the laboratory was unable to test for protein in CSF because they had run out of reagents.

TABLE 8. HIV STATUS OF THE 75 PATIENTS WITH MENINGITIS

SEX	HIV SEROSTATUS			
	HIV +VE %	HIV -VE %	UNKNOWN	TOTAL
Male	28 (62.22%)	10 (22.22%)	7 (15.56%)	45 (60%)
Female	28 (35.56%)	9 (20.0%)	5 (11.11%)	30 (40%)
Total	44 (58.67%)	19 (25.33%)	12 (16.0%)	100 (100%)

The HIV test was done on all of the 75 patients, but only results of 63 patients were received and 44 (28 males, 16 females) out of 63 were HIV +ve and 19 out of 63 were HIV-ve giving an overall sero positivity rate of 69% amongst the meningitis patients.

From the above results it may be shown that meningitis occurs more frequently amongst those that are HIV positive as opposed to those who are HIV negative.

Complications of meningitis were further analysed in association with the type of organism to find out which organisms were associated with severe disease and the following were observed:

TABLE 9. COMPLICATIONS OF MENINGITIS IN ASSOCIATION WITH ORGANISMS

COMPLICATION	ORGANISMS				
	Total	N Mengitidis	Str Pnuem	Crypt	Other
Seizures	7	3		3	1
Coma	8	2	2	4	
Cranial Nerve	6	2	2		2
Palsies					
Deafness	2	1	1		
Hemiplegia	4	1	2		1
Death	30				14
Paraplegia	2	1			1

Cryptococcal meningitis was associated with major complications followed by Neisseria Meningitides which was responsible for 2 cases of coma,3 cases of seizures, 2 cranial nerve palsies and one case of paraplegia.

The above analysis in this study showed that meningitis when it occurs in individuals who are HIV positive the disease is more fulminant and is associated with greater mortality than when it occurs in individuals who are HIV negative.

The summary of the major findings in this study were that:-

(1) The commonest cause of meningitis in those that were HIV positive in this study group was cryptococcal meningitis followed by Neisseria meningitides.

(2) The culture positivity rate was low in that out of a total of 59 turbid CSF only 15 were positive giving a 25% culture positivity rate which is very low as compared to the expected.

The hypothesis under study states that meningitis in HIV positive patients is more fulminant and associated with severe complications and higher mortality rates than meningitis in HIV negative patients.

To test the Null Hypothesis of there being no difference in clinical presentation and outcome in the two groups:

TABLE 10.

DATA FOR THE STUDY COMPARING NUMBER OF DEATHS IN HIV POSITIVE MENINGITIS CASES AND DEATHS IN HIV NEGATIVE MENINGITIS CASES:

STUDY GROUP	DEATH	NO DEATH	T O T A L
HIV POSITIVE	26	18	44
HIV NEGATIVE	4	27	31
TOTAL	30	45	75

EXPECTED TABLE		
17.7	26.4	44
12.2	18.6	31
30	40	75

The hypothesis states that there are more deaths in HIV positive meningitis patients than in HIV negative meningitis patients.

The first table shows data for the study comparing number of deaths in HIV positive meningitis cases and deaths in HIV negative meningitis cases.

The null hypothesis Ho:- states that there is no difference in rate of death in two groups using the chisquare test.

$$T = \frac{(O - E \mid - 0.05)^2}{\quad}$$

$$T = \frac{(26 - 17.1 \mid - 0.05)^2}{17.7} + \frac{(18 - 26.4 \mid - 0.05)^2}{26.4}$$

$$+ \frac{(4-12.2 -0.05)}{12.2} + (27 - 18.6 - 0.05)$$

$$T = \frac{(8.4 - 0.05)}{17.7} + \frac{(8.39 - 0.0.5)}{26.4} + \frac{(8.2 - .05)}{12.2} + \frac{(8.4.-0.05)}{18.6}$$

$$= \frac{69.7}{17.7} + \frac{69.7}{26.4} + \frac{69.7}{12.2} + \frac{69.7}{18.6}$$

$$T = 3.3 + 2.7 + 5.7 + 3.7 = 15.4$$

T = 15.4 which under Ho approximately follows a X^2 distribution
$X^2_{.95} = 3.84 < 15.4 = T$
$P < 1 - 0.95$
$P < 0.05$ is statistically significant

TABLE 11

DATA FOR THE STUDY COMPARING NUMBER OF PATIENTS THAT DEVELOPED COMPLICATIONS IN HIV POSITIVE MENINGITIS PATIENTS AND HIV NEGATIVE MENINGITIS PATIENTS.

STUDY GROUP	COMPLICATIONS	NO COMPLICATIONS	TOTAL
HIV +VE	38	6	44
HIV -VE	15	16	31
TOTAL	53	22	75

EXPECTED TABLE		
31	13	44
22	9	31
53	22	75

The hypothesis states that meningitis HIV +VE patients would be associated with more complications as compared to HIV-VE patients with meningitis.

The null hypothesis states that there is no difference in the number of complications in the two groups.

To test this null hypothesis Ho

$$T \text{ statistics} = (10 - E - |- 0.05)^2$$

$$= \frac{(38 - 31 \mid 0.05)^2}{31} + \frac{(6 - 13 \mid - 0.05)^2}{13} + \frac{(15-22 \mid - 0.05)^2}{22}$$

$$+ \frac{(16-9-0.05)^2}{9}$$

$$= \frac{(7-0.05)^2}{31} + \frac{(7.0.05)^2}{13} + \frac{(7.0.05)^2}{22} + \frac{(7.0.05)^2}{9}$$

$$T = \frac{48.3}{31} + \frac{48.3}{13} + \frac{48.3}{22} + \frac{48.3}{9}$$

$T = 1.56 + 3.7 + 2.2 + 5.36$
$T = 12.82$ which under Ho approximately follows X^2 distribution.

$X_{.95} = 3.84 < 12.82 = T$
$P < 0.05$ which is statistically significant

9.0 DISCUSSION:

9.1 The Population

During the four months study period beginning 1st December 1993 to 31st March 1994 a total number of 14,078 patients were seen and 5698 (44%) patients were admitted to the University Teaching Hospital, and 421 of these (7.4 %) were confirmed cases of meningitis. All the 421 were black Zambians. Of the 421 cases 277 were discharged but 144 cases died giving an overall case fatality rate of 34.2%. 32.4% for the Adults and 38% for the Paediatric group.

The distribution for the meningitis cases were as follows 256 adults and 165 children. Out of the 256 adults' cases a total number of 75 patients; 30 females and 45 males agreed to be interviewed and participated in the study.

The overall age range was 14 to 73 with an overall mean age of 27 years. The age range for the female patients was 18 years to 73 years with a mean age of 30 years while the age range for the male patients was 14 years to 48 years with a mean age of 29 years.

From the above it was noted that 57% of the adults patients were aged below 40 years but only 10.6% were below the age of 19 years. The finding is contrary to the findings in the review of literature were epidemic meningitis is a disease of the young adults and children. As well as the above, given that up to 50% of the Zambian population is under the age of 15. One would have expected a bigger proportion of the adult meningitis cases to be below the age of 20 years but this was not the case in this study

group.

Even though in this study group there were more males than females i.e 45 males and 30 females, the proportion of HIV positive patients in the two sexes was not statistically significant, in that out of 45 males, 28 were HIV positive = 62 % for the males and out of the 30 female patients 16 were HIV positive which works out to be 53%.

SPECIAL CLINICAL AND LABORATORY PRESENTATION

Clinical presentation of the two groups did not differ significantly in as far as symptoms of meningitis and duration of symptoms were concerned. However, the HIV positive patients appeared to be sicker and presented with other problems as well as the meningitis e.g. 20/44 = 45 of the HIV patients had oral candidiasis, 12/44 of the HIV patients had pneumonia.

The CSF microbiological reports showed that out of the 75 CSF specimens that were sent, only 65 were reported on: and out of these 65, 59 were reported to be turbid. However, only 15 of the 59 turbid specimens had positive culture reports. Gram stain on CSF also only picked up the 15 which were confirmed with culture which gave us a low positive culture rate of 23%. In most laboratories CSF culture is positive in 70 to 80% of cases. The low positive culture report is difficult to explain but it may be that, the major causes of meningitis in this sample may have been other organisms which could not be picked up on gram stain and probably would not grow on the 3 media that the CSF is plated on i.e. chocolate agar, blood agar and macconkey.

Nigrosin stain picked up cryptococcal neoformans in 14 specimens and all the 14 occurred in HIV positive patients.

The history in these patients was that of an acute onset of headache, fever, neckache and the range of duration of symptoms was 0 to 5 days which is in keeping with the acute bacterial meningitis. However the CSF findings of cryptococcus neoformans suggests that this opportunistic parasite is capable of producing acute symptoms in immune compromised hosts. The usual presentation of meningitis due to this organism is a chronic history of severe headache, that may or may not be associated with other symptoms of meningitis, and is usually associated with clear CSF. The finding of dual infection of bacterial and cryptococcus in the same patient in 4 of these patients whereby the CSF had both Neisseria Meningitides and cryptococcus neoformans may explain why the CSF was turbid even in cases where cryptococcus was isolated.

Dual infection in these patients is suggestive of severe immune compromisation on the part of these patients and has been found in terminal stages of AIDS patients.

OUTCOME

Analysis of the various variables showed that there was significant association between living in a high density population area and development of meningitis, and that over crowding was an important risk factor.

In the study there were more males than females i.e. 45 males and 30 females. However the proportion of HIV patients in sexes was

not statistically significant in that out of 45 males, 28 were HIV positive = 62% for the males, and 16 out of 30 for the females which works out to be 53%.

The mortality in HIV positive patients was much higher in that 26 out of the 30 deaths (86%) were HIV positive. The proportion of deaths in HIV positive patients was 26/44 = 59%.

The high mortality rates in these individuals may also be explained on the basis of the deranged immunity which may be associated with severe septicaemia and hence these patients are a lot sicker than the other patients, and hence unless if all these factors are taken into consideration meningitis in these patients would be fatal.

Being HIV positive and having meningitis was also associated with more severe complications ($P < 0.05$) as compared to the other group, and these complications were fatal. In this study the most significant complications were seizures, coma, hyperpyrexia, paraplegia, hemiplegia and severe uncontrollable epistaxis. The seizures that occurred in these patients may have been of multiple origin:

(a) Spread of infection from the meninges into the brain leading to meningoencephalitis,
(b) As a result of overwhelming infections patients may develop hypoglycemia which leads to seizures,
(c) Seizures in these patients may also be metabolic derangement associated with diarrhoea and vomiting which was present in 3 of these patients.

Coma in these individuals would equally be of multiple origin: Probably secondary to severe meningoencephalitis, hypoglycemia and metabolic derangement as above.
Epistaxis occurred in two patients who had meningococcaemia and may have been secondary to DIC (Disseminated Intravascular Clotting) which may deplete clotting factors leading to uncontrollable epistaxis. Epistaxis in AIDS patients may also be secondary to thrombocytopenia which has been identified in association with HIV infection and has been said to be of auto immune origin. The hyperpyrexia that occurred in two of these
patients may be explained on the basis of severe overwhelming infection which may interfere with temperature regulation in the hypothalamus.

The hemiplegia and paraplegia may also be of multiple origin:

(a) May be secondary to vascular occlusion by organisms, and microemboli that may occur with septicaemia and disseminated intravascular coagulation associated with meningococcaemia.

(b) Since these individuals are immunocompromised they are prone to infection with opportunistic organisms that may behave as space occupying lesions e.g. aspergillosis aspergillomas in the brain.
Toxoplasmosis and disseminated candidiasis.

The shock state that was noted in two of these may have been secondary to bacteriaemia/septicaemia and toxeamia that may be associated with meningococcal meningitis.

The clinical presentations and complications that were observed in these patients were in line with the hypothesis of this study, and there was a difference in the clinical presentation and the complications that developed in the HIV positive patients as compared to those that were observed in the HIV negative patients and this difference was statistically significant.

10. CONSTRAINTS/LIMITATIONS:

Initially this study had been designed to look at HIV/AIDS and Meningitis but ended up being a study of HIV/AIDS and Bacterial Meningitis. The INITIAL STUDY was felt to be an impossible study to do in this part of the world because:-

(1) Facilities are not available to diagnose the other causes of meningitis e.g. viruses, fungi, protozoa.

(2) In the absence of CT scan, it would be difficult to rule out other causes of meningitis and meningo encephalitis e.g. Toxoplasmosis. And complications of meningitis like hydrocephalus, brain abscess, subdural effuse and empyema.

(3) And to rule out other causes of the abnormalities that may be found in following these patients up. That is determining whether there are sequelae of meningitis, or complications of other retro viral related presentations.

4. Problem of follow-up:- Even though initially the study proposed that the patients be followed up for six months after discharge from hospital, this was an impossible

task to achieve, therefore patients were not followed up because (a) poor follow-up returns after discharge from hospital, (b) non-availability of funds to reimburse transport expenses incurred by patients.

5. Lack of funds to meet the budget for laboratory investigations resulted in the CSF protein not being analysed by the laboratory when the hospital reagents for CSF protein analysis ran out.

6. The study was conducted in a teaching hospital which is also a tertiary care facility for the country. This may have introduced bias in the study in that the patients that came to this institution may be sicker and with greater number of complications than may be expected in other institutions.

7. The fact that there was an interview before enrollment may also have introduced interviewer and interviewee bias into the study.

8. Pre-test counselling for HIV testing may also have introduced bias in the study in that only a selected population i.e. those that were willing to have the HIV test were included.

9. The poor culture positive results in the CSF specimens sent to the laboratory also have contributed to the poor specific diagnosis and hence some patients may have not received specific treatment which may have contributed to the poor outcome in some of the patients.

11.0 ETHICAL CONSIDERATIONS:

Patients recruited in the study already had meningitis at the time of admission and the investigations that they were subjected to were the standard investigations that patients who present with meningitis are normally supposed to have. When a patient with meningitis was identified, before being recruited into the study informed consent was obtained and pre-test counselling for HIV test done.

Patients were not subjected to any procedures that would have endangered their lives or harmed them in any way. As well as the above patients received the standard treatment given to all other meningitis patients.

CONCLUSIONS AND RECOMMENDATIONS:

The results showed that there is a statistically significant difference between the clinical presentation, progression and outcome of meningitis in HIV positive patients as compared to that of HIV negative patients.

This study has highlighted some of the areas that need to be addressed in dealing with meningitis patients who are also HIV positive.

The significant findings in this study point to the fact that even though meningitis is usually a medical emergency, it is even more so when it occurs in patients who are immunocompromised. This study has shown that the clinical presentation of meningitis in HIV patients is more fulminant and

was associated with severe complications and high mortality rates.

From the above it seems important that the management of meningitis should be modified in patients who are HIV positive. Taking into consideration the fact that the meningitis may be due to multiple organisms. The finding of one organism in CSF does not necessarily mean that, that is the organism causing the meningitis, there may be many more in the same patient. Management should be intense and watching out for all possible complications.

HIV Positive patients who present with meningitis should be put in the intensive care unit and monitored closely for they are prone to develop circulatory collapse, coma and shock. Management should therefore be anticipatory.

Rapidly acting bacteriocidal antibiotics need to be administered immediately without delay.

Recent studies have shown that these antibiotics may rapidly destroy bacteria and the breakdown products may be toxic to the brain and worsen the meningitis by production of cytokines, addition of corticosteroids to the regime may be beneficial to these patients. Glucocorticoid therapy has been observed to reduce the production of cytokines in the CSF, reduce the severity of the inflammatory process in the CSF and neurological sequelae.

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14.0 MASTER DATA SHEET

DATE	ID NO	FILE NO	SEX	AGE	SERO STATUS	LAB DIAG	COMPLICATIONS
17-12-93	01	154724	F	38	+	Neisseria Meningitides	Oral Thrush (R)Pnuem Comma Died
23-12-93	02	172988	M	17	+	Turbid CSF Pressure increased	
6-12-93	03	174945	F	20	-	CSF Clear no growth	Convulsions
14-12-93	04	176506	F	22	+	Turbid CSF No growth	
22-12-93	05	174198	F	73	-	CSF Turbid no growth	
26-12-93	06	177299	F	A	+	Turbid no growth WBC 380 40 60	
27-12-93	07	178261	M	14	-	Clear CSF no organisms	
27-12-93	08	177516	M	16	-	CSF cloudy	
15-12-93	09	176537	M	41	+	Clear no growth	RCC
27-12-93	10	177512	M	31	+	Traumatic Confusion Hyperpyrexia	
27-12-93	11	177394	M	22	+	CSF Xanthdchromic increased pressure seizure, disorders weakness both legs	
27-12-93	12	177396	M	21	+	CSF Turbid no growth SDA	
27-12-93	13	177268	M	40	-	CSF cloudy no organisms	
27-12-93	14	175773	M	A	-	CSF cloudy no organisms	
28-12-93	15	177576	F	20	+	Athritis confusian RCC Meningococcaemia Turbid Arthritis confusion Meningococcaemia Home	
27-12-93	16	177384	M		-	Cloudy no organisms	Died
27-12-93	18	177398	M		+	Cloudy no organisms	
27-12-93	19	181005	F		-	Clear no growth	home
10-2-94	20	184073	F	A	-	No growth clear	Home
13-2-93	21	183830	F	20	+	No growth CSF turbid convulsions	Home
7-1-94	23	178655	M	36	+	Cloudy no organisms	Died
21-3-93	24	187827	M	15	+	CSF No organisms cloudy Neisseria Mengitidis	
15-1-94	25	180092	M	48	+	Clear CSF No growth	Died
21-3-94	26	T/C	M	48	+	Cloudy no organisms	
11-3-94	27	190082	M	40	+	Crypto CSF cloudy	Died
30-3-94	29	189410	M	38	+	40 80 glu 2.5 2g/l 20	Died Hemiplegia
3-1-94	30	179197	F	18	-	CSF Turbid under pressure	
23-2-94	31	184792	F	20	+	Cryptococcous	Died
23-2-94	32	183928	F	32	-	Turbid CSF no growth	Convulsions
5-1-94	33	170891	F	26	+	g_ve Diplococci + Crypto	convulsions
23-2-94	34	184821	F	26	-	Cloudy CSF No organisms	
3-2-94	35	T/C	F	26		Cloudy CSF no organisms	
26-2-94	36	T/C	F	36	+	CSF Turbid Cryptococcous	Died
26-12-93	37	T/C	F	37	+	CSF Turbid prot 2.6 g/l	

6-12-93	03	174945	F	20	-	CSF Clear no Convulsions Growth
14-12-93	04	176506	F	22	+	Turbid CSF no growth
22-12-93	05	174198	F	73	-	CSF Turbid no growth
26-12-93	06	177299	F	A	+	Turbid no growth WBC 380 40 60
27-12-93	07	178261	M	14	-	Clear CSF no orgnisms
27-12-93	08	177516	M	16	-	CSF Cloudy Confusion
15-12-93	09	176537	M	41	+	Clear no growth RCC
27-12-93	10	177512	M	31	+	Traumatic Confusion Hyperpyrexia
27-12-93	11	177394	M	22	+	CSF xanthochromic increased pressure weakness both legs Seizure
27-12-93	12	177396	M	21	+	CSF Turbid no growth SDA
27-12-93	13	177268	M	40	-	CSF Cloudy no organisms
27-12-93	14	175773	M	A	-	CSF Cloudy no organisms
28-12-93	15	177576	F	20	+	Athritis confusion Meningococceamia Home
27-12-93	16	177384	M		+	Cloudy no orgnaisms
27-12-93	18	177398	M		+	Cloudy no organisms
27-12-93	18	181005	F		-	Clear no organisms Home
10-2-94	19					
13-2-94	20	183830	F	20	+	No growth CSF Turbid Convulsions Home
7-1-94	21	178655	M	36	+	Cloudy no orgnisms Died
21-3-94	22	187827	M	15	+	CSF Cloudy no organisms Neisseria Meningitides Died
15-1-94	23	180092	M	48	+	Died before lumbar puncture
21-3-94	24	T|C	M	48	+	Cloudy no orgnisms
11-3-94	25	190082	M	40	+	Cloudy no orgnisms Died
30-3-94	26	189410	M	38	+	40 80 glu 2.5 prot 2 g/l cryptococous Died
3-1-94	27	179197	F	18	+	CSF Turbid under pressure
23-2-94	28	184792	F	20	+	Cryptococous Died
23-2-94	29	183928	F	32	-	Turbid CSF no growth
5-1-94	30	170891	F	26	+	G+ve diplococci + Crto Convulsions
2-3-94	31	184821	F	26	-	CSF Turbid Cryptococcous Died
3-2-94	31	T/C	F	26		Cloudy CSF no organisms
26-2-94	32	T/C	F	36	+	Cryptpcpccous Died
26-12-93	33	T/C	F	37	+	CSF Turbid Prot 8.6g/l Died
1-3-94	34	T/C	F	34	+	Turbid Cryptococcous Yeast cells Died
7-1-94	35	T/C	M	A	+	Cloudy no orgnisms
4-3-94	36	T/C	F	51	+	Ga+ve Dippiococi
4-3-94	37	T/C	F	26	+	CSF Turbid growth Neisseria Streptococcous Pneumonia Died
30-12-93	38	T/C	F	43	+	Crypto Confusion Persistant fever
3-12-93	39	T/C	M	A	+	CSF Turbid no organisms
3-12-93	43	T/C	M	35		WBC 80 P 80 glu 3.8 Part* 20
17-1-94	44	181011	M	18	-	Neisseria Meningitids Paraplegia

25-2-94	45	135181	M	34	+	CSF Turbid P 30 70
28-2-94	46	185094	M	29	-	Meningococcaemia Died shock + Hypertension
1-3-94	47	T/C	F	52	+	Pneumococcal Meningitis
1-3-94	48	T/C	F	26	+	Neisseria + Candida Died
16-2-94	49	T/C	M	19	+	LP. Xanthochromic
16-2-94	50	159119B	M	36	+	Cryptococcal sugar 3 prot 1.75 died
13-1-94	51	180092	M	48	+	Died before lumbar puncture Died of fits
2-2-94	52	182747	M	21	-	LP not done Discharged
6-2-94	53	182966	M	22	+	Salmonella Sugar 31 Prot not done Discharged

UNIVERSITY TEACHING HOSPITAL
BOARD OF MANAGEMENT
HEALTH INFORMATION SYSTEMS DEPARTMENT
PAEDIATRICS STATISTICS FROM 1993 - 1994

OUT PATIENT ATTENDANCE

MONTH	1993	1994
JAN	3,074	3,334
FEB	2,996	3,347
MAR	3,000	3,828
APR	2,876	3.631
MAY	2,869	3,459
JUN	2,112	4,216
JUL	2,391	4,189
AUG	2,663	4,416
SEPT	2,861	5,192
OCT	3,713	6,192
NOV	3,243	6,628
DEC	3,569	5,419
TOTAL	35,569	54,419

ADMISSIONS

	1993	1994
JAN	1,705	1,383
FEB	1,412	1,133
MAR	1,374	1,212
APR	1,390	1,267
MAY	1,475	987
JUN	999	976
JUL	815	1,051
AUG	1,100	1,311
SEPT	1,380	1,792
OCT	1,750	1,808
NOV	1,670	1,836
DEC	1,970	1,798
TOTAL	17,049	16,554

CONSENT FORM

I ..... fully understand the nature of this study and has no objections in participating in the study.

I further know that the results of this test shall be kept confidential and that the samples collected may be used for any additional test that may be required.

Name: ..... Sign: .....

Witness: ..... Date: .....

Doctor's Name: .....

THE IMPACT OF HIV ON BACTERIAL MENINGITIS IN ADULT ZAMBIAN PATIENTS

ENROLMENT FORM

INCLUSION CRITERIA COMPLETED CI = YES 0 = NO

INFORMED CONSENT: .....

CLINICAL DIAGNOSIS OF MENINGITIS: .....

CONFIRMED BY CSF: .....

BLOOD FOR SEROLOGY OBTAINED: .....

PATIENTS INFORMATION: .....

STUDY NUMBER: (01 - 250): .....

1. NAME: ..... HOSP NO: ..... WARD.....
2. DATE OF ENROLMENT (dd/mm/yy): .....
3. SEX (1 = MALE, 2 = FEMALE): .....
4. AGE (AT LAST BIRTHDAY): .....
5. NATIONALITY: .....
6. ETHNICITY: .....
7. RELIGION: .....
8. RESIDENTIAL AREA: ..... HIGH: .....LOW: .....
9. NUMBER OF ROOMS IN CURRENT HOUSE: .....
10. NUMBER OF PERSONS IN CURRENT HOUSE: .....
11. MARITAL STATUS: SINGLE .....

MARRIED .....

WIDOWED (cause of death)

12. EXTRA MARITAL SEXUAL ACTIVITIES: NUMBER OF PARTNERS: .....

PERMANENT: .....

CASUAL: .....

13. SOCIAL HABITS:

SMOKE: ..... NO ..... YES ..... CIGARETTES PER DAY

DRINKS: ..... NO ..... YES ..... BEER BOTTLES/DAY
TOT/DAY
CHIBUKU/DAY
BOTTLES OF KACHASU/DAY

14. EDUCATION COMPLETED: ..... 0 = NONE
1 = PRIMARY
2 = SECONDARY
3 = COLLEGE/UNIVERSITY

15. OCCUPATION/EMPLOYMENT: .....

16. MONTHLY TOTAL HOUSEHOLD INCOME: ..... KWACHA PER MONTH

<u>DURING THE LAST SEVEN DAYS</u>

17. CONTACT WITH PATIENT WITH MENINGITIS (1 = YES 0 = NO)

DATE .....

18. HISTORY OF ATTENDING BIG GATHERING IN PREVIOUS WEEK:

(a) FUNERAL 1 = YES, 0 = NO. How many days ago .....

(b) WEDDING

(C) RALLY

19. OTHER ILLNESS THAT MAY PRECEDE MENINGITIS: .....

.....

20. HISTORY OF HEAD TRAUMA (1 = YES, 0 = NO) DATE: .....

21. PNEUMONIA (1 = YES, 0 = NO) ..... DATE OF ONSET .....

22. APPROXIMATE DATE OF ONSET OF SYMPTOMS OF MENINGITIS:

.....

23. TIME FROM ONSET TO ENROLLMENT:

< 3 DAYS ..... > 3 DAYS .....

PART B: CLINICAL FINDINGS

A. SYMPTOMS AND SIGNS

24. HIGH FEVER (1 = YES 0 = NO) NUMBER OF DAYS: .....

25. CILLS (1 = YES 0 = NO) .....

26. HEADACHE (1 = YES 0 = NO) ..... (Number of days) .....

27. DNECKACHE/NECK STIFFNESS (1 = YES 0 = NO) Number of days .....

28. BACK PAINS (1 = YES 0 = NO) Number of days of back pain

.....

29. EXTREMITY PAINS (1 = YES 0 = NO) Number of days of extremity pains .....

30. NAUSEA = VOMITING (1 = YES 0 = NO) Number of days of nausea and vomiting .....

31. CONFUSION (1 = YES 0 = NO) Number of days of confusion ....

32. DELIRIUM (1 = YES = NO) Number of days of delirium .....

33. SEIZURES (1 = YES 0 = NO) Number of days of seizures .....

34. COMA (1 = YES 0 = NO) Number of days in coma .....

35. SHOCK (1 = YES 0 = NO) Number of days of shock .....

36. POSITIVE KERNIG SIGN (1 = YES 0 = NO) .....

37. POSITIVE BRUDZINSKI SIGN (1 = YES O= NO) .....

38. TEMPERATURE ON ADMISSION: .....

39. PURSE ON ADMISSION: .....

40. BLOOD PRESSURE ON ADMISSION: .....

41. PETECHIAL RASH (1 = YES 0 = NO) SITE: .....

42. ARTHRITIS (1 = YES 0 = NO) .....SITES .....

43. FOCAL NEUROLOGICAL DEFICITS (1 = YES 0 = NO) .....

44. DESCRIPTION .....

45. LYMPHADENOPATHY (1 = YES 0 = NO) ..... SITES .....

DESCRIPTION .....

46. EVIDENCE OF HERPES ZOSTER INFECTION (1 = YES 0 = NO)

SITES .....

47. OTHER SKIN LESIONS (Describe): .....

48. NAIL CHANGES (a) Yellow disceleration (1 = YES 0 = No) .....

(b) Longitudinal lines (1 = YES 0 = NO) .....

(c) Brown pigment (1 = YES 0= NO) .....

(d) Other (describe) .....

49. HAIR CHANGES (1 = YES 0 = NO) .....

50. ORAL THRUSH (1 = YES = NO) .....

PART C: LABORATORY DATA

51. LUMBAR PUNCTURE CEREBRAL SPINAL FLUID RESULTS

- APPEARANCE
- PRESSURE
- GLUCOSE
- PROTEIN
- CELL COUNT WBC TOTAL: .....

POLYMORHO NUCLEAR CELLS .....
LYMPHOCYTES .....
ROSINOPHILS .....
RED BLOOD CELLS .....
OTHER ..... GRAM STAIN

GRAM NEGATIVE INTRACELLULAR DIPLOCOC
(1 = YES 0 = NO) .....

EXTRACELLULAR DIPLOCOCCI
(1 = YES 0 = NO) .....

GRAM POSITIVE DIPLOCOCCI (1 = YES 0 = NO)

.....

GRAM NEGATIVE PLEOMORPHIC RODS
(1 = YES 0 = NO) .....

- CULTURE REPORT .....
- SENSITIVITY REPORT .....

52. BLOOD CULTURE RESULT .....

CLINICAL PROGRESSION

	DAY (1)	DAY (2)	DAY (3)	DAY (4)	DAY (5)
GENDERAL CONDITION	.....				
TEMPERATURE	.....				
NECK STIFFNESS	.....				
PETECHIAL RASH	.....				
SHOCK	.....				
FOCAL NEUROLOGICAL DEFICITS	.....				
DERILIUM	.....				
CONFUSION	.....				
COMMA	.....				
COMPLICATIONS	.....				
SPECIFY	.....				
	.....				