CLINICAL UTILITY AND COST EFFECTIVENESS

OF CSF TB BACTEC MGIT CULTURES IN THE

EVALUATION OF HIV PATIENTS WITH

MENINGOENCEPHALITIS AT THE

KENYATTA NATIONAL HOSPITAL.

A dissertation submitted in part fulfillment of the requirements for the degree of
Master of Medicine in Internal Medicine by:

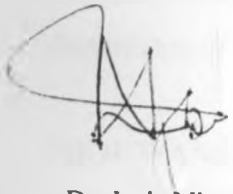## DR. LOIS N. WAGANA

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DECLARATION

I certify that this dissertation is my own original work and has not been presented for a degree at any other university.

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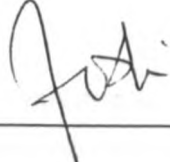
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DEDICATION:

To my grand father, who constantly urged me to pursue this degree.

To my parents, brother, sister and friends, whose tremendous encouragement has motivated me to keep at it.

To my God who has made it possible.

ACKNOWLEDGMENTS:

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I am truly grateful.

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LIST OF ABBREVIATIONS:

A.A.F.B	: Acid Alcohol Fast Bacilli
AIDS	: Acquired Immune Deficiency Syndrome
C.E.A	: Cost Effectiveness Analysis
CSF	: Cerebrospinal Fluid.
D.N.A	: Deoxyribonucleic Acid.
ELISA	: Enzyme Linked Immunosorbent Assay
GCS	: Glasgow Comma Scale.
HIV	: Human Immunodeficiency Syndrome.
KDHS	: Kenya Demographic and Health Survey.
KEMRI	: Kenya Medical Research Institute
K.N.H	: Kenyatta National Hospital.
L.P	: Lumbar puncture
MGIT	: Mycobacterium Growth Indicator Tube.
MOH	: Ministry of Health.
M.O.T	: Mycobacteria other than TBM.
M.R.C	: Medical Research Council
M.T.B	: Mycobacterium Tuberculosis.
NASCOP	: National AIDS and STI Control Program
NLTP	: National Leprosy and Tuberculosis Program
PCR	: Polymerase Chain Reaction
PI	: Principal Investigator
PLWA'S	: Persons Living with HIV AIDS.
R.N.A.	: Ribonucleic Acid.
SSA	: Sub Saharan Africa.
TB	: Tuberculosis.
TBM	: Tuberculous Meningitis.
WHO	: World Health Organization.
ZN	: Ziehl Neelsen stain for A.A.F.B

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1.0: ABSTRACT

Background:

The spread of HIV epidemic has contributed immensely to an increase in the annual incidence of Tuberculosis (TB) and especially of extra-pulmonary TB in Kenya.[1] The diagnosis of Tuberculous Meningitis (TBM) is difficult, usually empirical, delayed and is associated with high mortality, which can be reduced by initiation of therapy in the earlier stages of disease.[2] Traditional solid culture methods have a sensitivity of 50 to 70% and take 4 to 8 weeks to yield results. Liquid BACTEC culture media have a sensitivity of 95% and take between 48hrs and 21 days with an average time of 7- 14 days to give a result. Though costly, they potentially would offer an advantage of early diagnosis, treatment and positive impact on, morbidity and mortality from TBM.

Objective: To determine the clinical utility and cost effectiveness of early CSF BACTEC cultures among HIV positive patients who present with features of meningoencephalitis at K.N.H.

Study design: Hospital based comparative In-patient cohort study.

Methodology: Patients admitted with a diagnosis of meningoencephalitis were screened for HIV on the morning following admission. Those who tested positive and met inclusion criteria were recruited consecutively and randomized to either BACTEC or Usual Care arms. All patients received the usual care for meningitis as deemed necessary by their primary care physicians. Those in the BACTEC arm had, in addition to their usual workup, a Mycobacterial Growth Indicator Tube (MGIT) BACTEC culture done on their CSF for TBM, on the morning immediate post admission. All patients were followed up for a period or 4 weeks in hospital stay or up to death or discharge whichever was sooner. Time to definitive diagnosis of TBM by positive culture result, time to initiation of anti-TB therapy and time to discharge were studied. Initiation of anti-TB was at the discretion of the clinical care team and was not study directed.

Results: A total of 219 patients were screened. Of these, 142 were included into the study, 89 in the BACTEC arm and 53 in the usual care arm. Male patients were 70 (49.3%). The mean age was 37.2 years, range 13 and 62 years. Of those in the BACTEC arm, 9 (10%) had a positive CSF culture at 21 days and 14 (15.7%) at 8 weeks. The average time to culture positivity was 12 days, ranging between 5 and 40 days. Time to starting anti-TB therapy ranged from 1 to 22 days, with a mean of 4.99 days. The decision to start anti-TB was made empirically in all the patients, at the discretion of the clinical care team and was not influenced by the findings of the study. The average duration of hospitalization for discharged patients was 11.92 days, 10.56 and 14.48 in the BACTEC and usual care arms respectively, with a statistically significant difference in duration of hospital stay between the two groups; p=0.001. Total hospital mortality was 65 (45.8%). There was no statistically significant difference in mortality between the BACTEC and usual care arms. Average time to death was 7.5 days from admission, 6.93 in the BACTEC arm and 8.9 in the usual care arm, p=0.108.

Conclusion: Among the HIV positive patients with meningoencephalitis, the prevalence of TBM by BACTEC culture was found to be 15.7%. There is no statistically significant difference in time to diagnosis, duration of hospital stay, mortality and morbidity between the BACTEC and usual care arms. It is therefore not cost effective to perform a BACTEC culture in these patients, for the purpose of early diagnosis and treatment of TBM.

2.0: LITERATURE REVIEW:

2.1: Introduction:

TB has been with mankind for many centuries. Indeed it has been found in Egyptian fossils dated as far back as 3500BC. [2] The infecting organism; *Mycobacterium tuberculosis* (M.T.B), was first isolated by Professor Robert Koch in 1882. It is classified under the family Mycobacteriaceae and in the order Actinomycetales.

M.T.B belongs to the *Mycobacterium tuberculosis complex*, being the most important agent of morbidity and mortality in this group. Other organisms in this complex include *M. bovis, M. africanum, M. microti* and *M. canetti*. M.T.B is a rod shaped non spore forming aerobic bacillus. measuring 0.5µm by 3µm, in size and stains neutral on gram stain. It does not decolourise on washing with acid or alcohol and is therefore referred to as Acid Alcohol Fast Bacillus, A.A.F.B.

2.2: Disease Burden:

TB. is the second most common cause of infectious disease related deaths worldwide, being second only to HIV/AIDS.[4] In the year 2001, over 3.8million new cases of TB were reported worldwide, 90% of these being from the developing world. The World Health Organization (WHO) estimated an under reporting rate of >50% for new cases and postulated that 8.5 Million new cases had occurred that year. Of these, it is was estimated that 5 M occurred in Asia, 2 M in Africa, 0.6 M in the Middle East and 0.5 M in Latin America. [5]

In Kenya, the annual notification rate of Tuberculosis has been on the increase; increasing in 2004 by 16%, from the previous year.[1] The annual case notification rate has increased nine fold from 53/100,000 in 1990 to 320/100,000 in 2004. The total number of new cases also increased nine fold, from 11,625 in 1990 to 105,783 during the same period of time, with a peak age between 25 to 34 years and a male to female ration of 1.6:1.[1] The graph below depicts the recent trends in the prevalence of TB in Kenya, between 1990 and 2003.
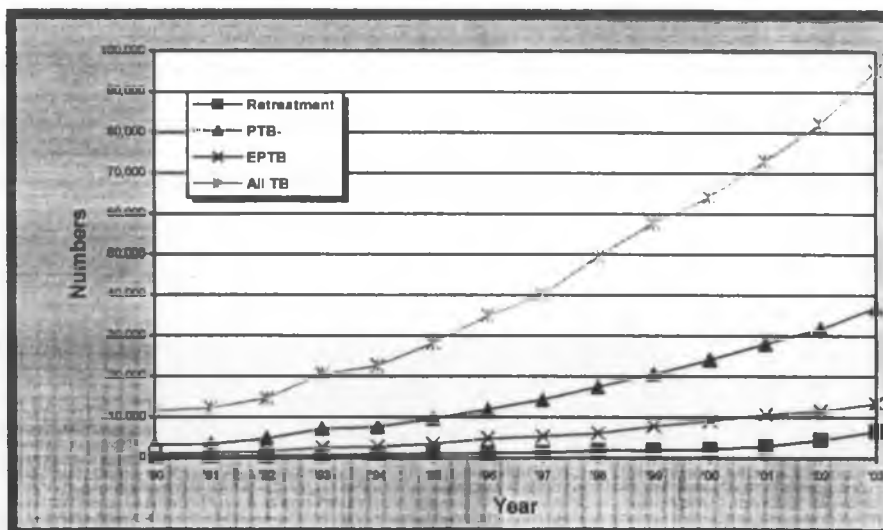
Fig. 1: Prevalence of TB in Kenya, 1990-2003: N.L.T.P. Kenya.
Re-treatment; persons developing TB within a year from completion of anti TB
treatment, PTB; Pulmonary TB, EPTB; extra-pulmonary TB.

2.3: HIV/ AIDS Pandemic:

The WHO has declared HIV/AIDS a global emergency. An estimated 42M people are
infected with HIV worldwide. 69 percent of these; 29M, are from Sub Saharan Africa
(SSA). [6]

In Kenya, an estimated 1.1M people are living with HIV/AIDS and another 1.5 Million
have succumbed to HIV related causes since the early 1980's.[7] The annual death rate
from HIV/AIDS in Kenya is at an all time high of 150,000 persons per annum. This is
thought to be subsequent to the high infection rate of 200,000 per annum that was
experienced in this country in mid to late 1990's and has resulted in a reduction in
Kenyan life expectancy from 65yrs in mid 1970's to 46years presently. [7]
Fortunately, the prevalence of HIV in Kenya is now on the decline from a prevalence of
10% in 1995 to 6.7 presently, with a regional variation of 1- 15%. In Nairobi, the
prevalence of HIV is 10%.[8] The graph below depicts the relationship between HIV
infection and AIDS related deaths in Kenya.

As is stated above, there is an increase in mortality from HIV, which reflects a relationship between the increased incidence of new HIV cases in the mid 1990s. It would be expected that since progression to full blown AIDS takes between 3 and 10 years, the peak in mortality from AIDS would be seen in the early years of the 21st century.
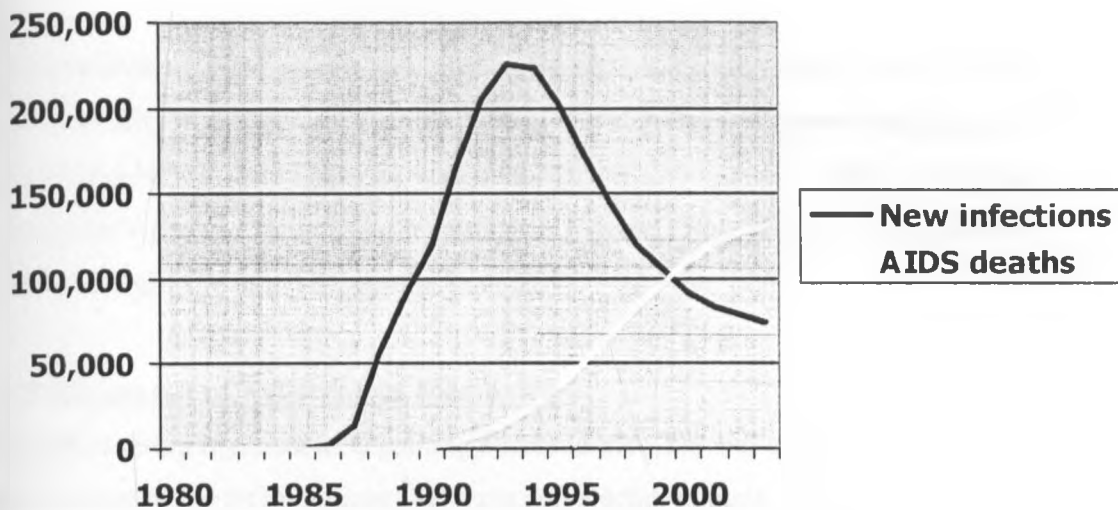
Fig. 2: HIV infections and AIDS related deaths; persons per year in Kenya
   N.A.S.C.O.P, 2003.

2.4: HIV / TB Interaction:

The presence of HIV infection is associated with a significant increase in the risk of TB. People living with AIDS (PLWA'S), have a 50% lifetime risk of TB in comparison to 5-10% in persons without HIV infection. This reflects a ten fold increase in the lifetime risk of TB.[2, 9] HIV is the single most important risk factor for TB presently. [2, 4, 9,11.]

Van Gorkom et al, in 1998, found a 40 percent prevalence of HIV infection among new cases of TB in Kenya, with a regional variation of 11.8-79.6%.[10] Data from the Ministry of Health (MOH) shows that in Kenya, Tuberculosis is the leading cause of death among People living with HIV/AIDS (PLWA'S). [6]

Extra pulmonary TB occurs with increased frequency among HIV infected persons.[11] Berenguer et al found a 59 percent HIV prevalence among patients with Tuberculous Meningitis (TBM), and a five fold increase in the incidence of tuberculous CNS infection in HIV infected persons as compared to HIV negative persons.[12] Hooker et al in 1998, found an 80 percent prevalence of HIV infection in patients with TBM, at Kenyatta National Hospital (K.N.H).[13]

The prevalence of TBM among HIV positive patients has been found to be 5.5%, in all cause morbidity in a Nigerian hospital. [14] Hakim et al found a 12 percent prevalence of TBM among HIV infected persons with meningitis in Zimbabwe.[15] Silber et al found 9 out of 38 HIV positive patients with meningitis to have TBM, giving a prevalence of 23.5% in a high HIV and TB prevalence area.[16]

2.5: Pathogenesis of Tuberculous Meningitis:

TBM results from mycobacteria gaining access to the CNS and causing intense inflammation of the leptomeninges, The pia and arachnoid mata. [2] The CNS is not the site of primary infection with M.T.B, but is involved when infection spreads from elsewhere in the body. This may occur during the primary infection or during reactivation of latent infection. [2, 3]

During primary infection, M.T.B gains entry into the body primarily through droplet inhalation from a sputum positive subject. Rarely, primary infection with M.T.B may occur via the gastrointestinal tract after ingestion of contaminated food or drink, as is the case with *M. tuberculosis var bovis.*

The inhaled mycobacteria are engulfed by the alveolar macrophages and are transported to the hilar lymph nodes. During this process, a transient bacillaemia occurs, with seeding of tiny Mycobacterial foci throughout the body.

In the CNS, these foci may be deposited in the sub-ependymal and sub-pial spaces, as well as in the meninges or on adjacent bone, where they remain as dormant foci of calcified Mycobacteria, whose proliferation is prevented by an intact immune system. [2,

[17,25] These foci were originally described by Rich and McCordick and are referred to as Rich foci. [2]

In the immunocompetent individual, the Rich foci are of no consequence, but remain in a latent phase, in a status quo, as it were, with the immune system. However, in states where cell mediated immunity is compromised such as occurs with HIV infection, diabetes mellitus, advanced age and with steroid or other immunosuppressive therapy, the Rich foci enlarge. Rupture of these into the sub-ependymal space leads to the severe inflammatory reaction characteristic of TBM. More deep seated Rich foci may enlarge to become tuberculomas or brain abscesses.

2.6: Pathophysiology:

The spillage of tuberculous protein into the sub-arachnoid space from rapture of Rich foci provokes an intense hypersensitivity reaction and inflammation of the meninges. This is especially so of the leptomeninges; the pia and arachnoid mata. Occasionally, the ventricular system and the choroid plexus may be involved.[18] A thick gelatinous exudate forms from this inflammatory process and is responsible for much of the clinical picture. This meningial exudate is most intense at the basal cisterns and spreads along the sylvian fissures.[18] The leptomeninges often have milliary tubercles; tiny clusters of mononuclear cells with central caseation. Unlike in the granulomas of primary infection, giant cells are rare.[19] The resultant pathophysiology may be explained on the basis of vasculitis, adhesions and encephalitis.

Vasculitis:

The thick gelatinous exudate from the intense inflammation within the sub-arachnoid space infiltrates adjacent cortical and meningial blood vessels, resulting in endothelial inflammation. This leads to obstruction of the arterioles with resultant compromise in blood supply to the distal brain parenchyma. This may manifest as transient neurological deficit, from ischemia or may result in brain infarction, where there is more extensive and sustained compromise in perfusion. [2] Patients often present with focal neurological deficits that simulate cerebrovascular accidents. The thalamus is particularly prone to the

delirious effects of vasculitis because of the tiny blood vessels that perfuse it. Bilateral thalamic infarcts are not unusual, in the setting of TBM.

Adhesions:

The thick gelatinous exudate that forms secondary to TBM is very rich in protein. It organises with ease during which process it fibroses and contracts. In the base of the brain, the organising exudate exerts traction to the cranial nerves, especially the oculomotor, abducent and facial nerves. These nerves may be involved collectively or in isolation, manifesting clinically as cranial nerve palsies. Early diagnosis and treatment with adjuvant steroids helps minimise or avoid this complication, by reducing the inflammation.[2, 17]

Encephalitis:

During the inflammatory response to tuberculous protein, oedema of the brain parenchyma results in encephalitis. Spread of this inflammatory process to the spinal cord may occur, with a concurrent myelitis. The inflammatory reaction on brain and spinal cord parenchyma is not very marked, however, but toxic degeneration of neurons may occur.[19] Patients present with a wide spectrum of clinical manifestations ranging from mild confusion to a comatose state.

Deep seated Rich foci within the brain parenchyma enlarge with resultant pressure effect. They may take the form of tuberculomas, which are solid casseous masses or may become tuberculous abscesses. These often cause mass effect and precipitate focal neurological deficits or hydrocephalus.

2.7: Clinical Presentation:

The clinical presentation of TBM is varied and largely depends on the stage of illness at which the patient presents.[2] The Medical Research Council of the United Kingdom developed a classification system for patients with TBM.[3] It consists of three stages; A, B, C, depicting advancing disease and portending a worsening prognosis for the advanced stages. The table below summarises these stages.

STAGE A	Insidious onset malaise, lassitude, low grade pyrexia, irritability, personality change. No alteration in level of consciousness. May have signs of meningial irritation.
STAGE B	Patients exhibit signs of meningial irritation. Headache, vomiting, alteration in level of consciousness, mental confusion. There may be signs of focal neurological deficit.
STAGE C	Signifies severe disease. Stupor or comatose, convulsions, hemi paresis, paraplegia, quadriplegia, involuntary movements.

Table 1: The MRC staging for tuberculous meningitis.[2]

Stage A: Is also known as the prodromal phase. It has an insidious onset and typically lasts between 2 to 3 weeks. Non specific symptoms such as malaise, lassitude, low grade pyrexia and irritability tend to dominate the picture. The patient is lucid and well oriented.

Stage B: The meningitic phase follows the prodromal phase. As the meningial inflammation progresses, more pronounced features of meningitis and meningo-encephalitis are appreciated. Headache, vomiting, confusion occur. Varying degrees of cranial nerve palsies may be present as may be long tract signs.

Stage C: Is the paralytic phase. It is characterised by a rapid acceleration in progression of the illness. A severely ill patient is encountered, confusion progresses to coma, with focal neurological signs, indicative of raised intracranial pressure. Kussmal's breathing is not unusual and papilloedema occurs. During this phase, the Syndrome of Inappropriate ADH Secretion may occur, leading to hyponatraemia.[3, 17, 18, and 19]

Death often ensues, between 5 to 8 weeks from the onset of illness. At K.N.H, mortality form TBM has ranged from 43 to 47 percent (K.N.H medical records, unpublished data). In their study at K.N.H, Hooker et al found an average duration of illness at presentation to be 65.2 days with a range of 37.6-92.9 days, among patients with definite TBM. They also found the commonest symptoms to be fever and night sweats, in 91.4% of the patients studied. They found night sweats in 81% of patients.[13] Nabil et at found a range of 7 to 90 days for symptoms of TBM. [16] In one study, Berenguer et al found fever, headache and altered consciousness to be the most common signs of TBM, in Madrid.[12] In addition, choroid tubercles may be seen on fundoscopy, in the individual who has disseminated TB. These may be seen in up to 20% of TBM patients. Hooker et al found choroid tubercles in 1 patient with TBM (3.8%).[13]

Where lumbar puncture is feasible and safe, the appearance of the C.S.F may give a clue as to the presence of TBM. Opening pressures may be normal or elevated in the TBM patient. C.S.F is usually cloudy in appearance and easily forms a fibrin clot if allowed to stand for a few minutes. This is because of the high protein content from the intense meningeal inflammation.

2.8: Prognosis
TBM is associated with a high morbidity and mortality rate, causing death and disability in >50% of affected patients. The outcome is better when treatment is commenced early.[20, 25]

2.9: Laboratory Diagnosis:
C.S.F evaluation offers the possibility of confirming the diagnosis.

2.9.1: C.S.F Microscopy:
Staining for A.A.F.B may be done. The Ziehl Neelsen (ZN) stain for A.A.F.B microscopy is widely available for microscopic identification of mycobacteria. An alternative staining method is the Kinyoun method. These, unfortunately have a low

yield. Hooker et al found a positive yield of 3.8 percent in his study. Berenguer et al found a positive A.A.F.B C.S.F smear in 22% of patients studied.[12]

2.9.2: C.S.F Cell Count:

Normal C.S.F contains up to 5 leucocytes per ml. Meningial inflammation results in an increase of leucocytes in the C.S.F. The T.B.M patient typically has increased lymphocytes in the C.S.F. However, in the early phase of illness, the C.S.F leucocytosis is predominantly a neutrophilia. After commencing therapy, there may be a transient elevation in C.S.F neutrophil count, the so called "therapeutic paradox".[17, 18]

Thwaites et al, in their study of 96 HIV infected patients with TBM found an average C.S.F lymphocyte count of 90 with a range of 5-100 cells per ml of C.S.F. In the same group of patients, the C.S.F average neutrophil count was 10 cells per ml with a range between 0-100.[11] Berenguer et al found a C.S.F leucocytosis of 234 cells per ml, with a range of 0 to 1,200.[12]   Hooker et al found an average cell count of 140 cells per ml in patients with definite TBM.[13]

2.9.3: C.S.F Biochemistry:

Evaluation of C.S.F protein concentration assists in strengthening the clinical suspicion for TBM. Protein concentration markedly above the normal upper limit of 0.45g/l tends to be the norm, in these patients.

In their study, Berenguer et all found an average C.S.F protein of 0.52g/l, with a range of 0.1-3.0. Thwaites et al found a range of 0.0 to 5.0; with an average of 1.3g/l. They also demonstrated that in a cohort which was HIV sero-negative, much higher values were obtained.[11] In their study, Honsoglu et al noted an average C.S.F protein of 2.4g/l, ±1.9g/l. [25]

C.S.F glucose in the TBM patient is typically low. Levels below 40% of serum glucose are often seen. In Berenguer's study, an average C.S.F glucose of 1.3 mM/l, with a range of 0.0-2.7 mM/l was found with 14% of patients studied having C.S.F glucose >2.2 mM/l.

2.9.4: Molecular Biological Approaches:

These are based on the principle of gene amplification. They include techniques such as the Strand Displacement Amplification, SDA, the Polymerase Chain Reaction, PCR, the Transcription Mediated Amplification (TMA) and the Q-Beta Replication Amplification. [26] Of these, the PCR is the most widely studied and used.

Polymerase Chain reaction:

Polymerase chain reaction on C.S.F for M.T.B has been tried. Both DNA and RNA PCR may be used. Its short time to results would conceivably offer an opportunity for quick diagnosis. Findings from different investigators have been disparate. Seth et al found 85% sensitivity among patients with meningitis and 95% sensitivity among patients with a high clinical probability of TBM. [27] In contrast, Bonington et al found a sensitivity of only 17.5% for RNA PCR on C.S.F from 89 patients treated for TBM.[28]
This low sensitivity makes it unsuitable for use as a screening test.

Miorner et al found 83% sensitivity for DNA PCR in comparison to solid culture media and 57% sensitivity compared to autopsy proven TBM. [29]

Chromatography:

High performance liquid chromatography utilising the Sherlock Mycobacteria Identification system (SMIS) is also in use. It offers rapid and accurate diagnosis but lacks in sensitivity and is not widely available for clinical use.[26]
Gas chromatography for Tuberculostearic acid has also been tried. Like liquid chromatography, it is not widely available for clinical use. [26]

Mycobacteriophage based methods:

This is a Phage amplified biological assay, the Mycobacteriophage D29. It has a sensitivity of 31% and a specificity of 86.1% for sputum specimens. It is unsuitable for screening due to its low pick up rate.[30]

Another Phage based assay, the Fast plaque TB assay has been tested for direct detection of M.T.B in sputum specimens. Its sensitivity was found to be 70-75.2% with a specificity of up to 99% in two separate studies. It has the advantage of ease of use, but is not yet widely available.[31, 32]

Immunodiagnostic tests:

These may be antibody or antigen based.[33] The diagnostic challenge with these is their inability to differentiate between exposed and infected persons.[34]

Antigen detection tests may utilise sandwich ELISA, inhibitor ELISA, and latex agglutination and reverse passive hemaglutination tests. A study on dip stick ELISA on urine specimens showed sensitivity of 93% and a specificity of 95%. This may be tried on C.S.F in future. [26].

Worth special mention on the antibody assays is the TB STAT PAK, a chromatographical assay that differentiates between active and dormant TB, from serum or whole blood or plasma. It was shown to have a sensitivity of 77.3% and a specificity of 28%. Its use for testing C.S.F samples has not been shown. [35]

2.9.5: C.S.F Culture:

This remains the gold standard for diagnosis of TBM. Traditional culture media, the L.J. and the Middlebrook 7H10 or 7H11 have a sensitivity of up to 80%.[20] They have the disadvantage of long recovery times of 4 to 6 weeks. Though reliable, they are not useful in the early detection of T.B.M.

Liquid TB cultures by the BACTEC MGIT method have the highest sensitivity available, of 90%, with a specificity of about 99%. They require significantly less time than solid media. Results are obtained between from as little as 48 hrs to 21days, with an average time of 7 to 14 days. Solid media in contrast, take at least 4 weeks and up to 8 weeks to yield results.

The BACTEC MGIT method relies on fluoroscopic assessment of reduction of oxygen concentration in a culture bottle into which the specimen has been inoculated. The obtained growth is confirmed as TB either by staining and microscopy, or by subculture on solid media. This technology is fairly new. For this reason, the cost of BACTEC MGIT cultures is still high. There may be a potential benefit in carrying out BACTEC cultures early, on patients with meningoencephalitis and HIV despite the extra cost, as it would provide an opportunity for early diagnosis of a condition that is difficult to diagnose and that has better outcomes if intervention is offered early.

Culture of C.S.F by liquid media, i.e. the BACTEC MGIT system, has consistently been shown to be the most sensitive means by which to isolate the organism, with a sensitivity of up to 96%. [13, 21, and 22]

In addition to its high sensitivity, the BACTEC MGIT 960 system has potential for cost effectiveness due to its high capacity. It can therefore be used in laboratories that handle a large number of specimens. [37]

Other liquid culture methods are the Septi Chek AFB, a non radiometric Biphase culture system, the MB/ BacT system and the ESP culture system. These have similar detection times as the BACTEC system. [26]

2.10: Concept of Cost Effectiveness Analysis:
Health care interventions may be evaluated with regard to their utility. If a health care intervention is effective in giving a desired outcome and is also affordable, then its implementation is acceptable, as it is deemed to be cost effective. It may be adopted as the standard of care against which new forms of intervention are measured.

One way to assess such new interventions is by carrying out a cost effectiveness analysis (C.E.A.). In this form of evaluation, two forms of intervention both leading to a similar outcome are measured against each other to see which will cost less. The new form of intervention is measured against the usual form of health care. If the proposed new form

of health care is found to be cheaper but leading to the same outcome, then it is said to be cost effective and is preferred over the usual care. In this case, it may be adopted as the new standard of care. If it is found to be more expensive to lead to the same outcome, then it is said not to be cost effective.

Cost effectiveness evaluations asses the gains versus costs of carrying out a set of activities or forms of intervention.[39] A C.E.A examines both cost and consequences of health programmes or forms of treatment. It compares the cost and outcome of one, usually the newer intervention, against the cost and outcomes of an established mode of intervention, the usual care. Assessment of cost effectiveness is done based on one or several outcomes of interest such as lives saved, morbidity gain, cases detected early, cost of hospitalisation, to name a few.

For example, in a certain hospital, the standard of care for patients with osteoporotic hip fractures has been skin traction. A study done elsewhere seems to suggest that carrying out hip replacement surgery early for these patients, results in their early mobilisation. The hospital administration receives this information with interest and notes tat perhaps this would translate to a reduction in cost incurred in the management of patients with these fractures because traction requires a long period of hospitalisation. They are considering adopting hip replacement surgery as the standard of care for these patients. Though it is appreciated that the hip replacement surgery is expensive, it appears that in the long run, it may be cheaper than treatment by skin traction.

A C.E.A should be carried out in this scenario; to find out how the hip replacement surgery compares with the usual care, with regard to cost. The desired outcome for both forms of intervention is mobilisation of the patients. In this C.E.A, one arm of patients undergoes usual care that is skin traction, while the other arm undergoes early hip replacement surgery soon after admission. The cost incurred to achieve the outcome is compared between the two groups. In the standard of care arm, the average cost for patients for whom the desired outcome is achieved is calculated, based on the average

duration of hospitalisation multiplied by the daily charges. In the surgery arm, the same cost measure is used. In addition, the average cost of surgery is added.

In this example, it may be found that surgery leads to early ambulation for patients from the usual 12 weeks to 1 week. Despite the high cost of surgery, the average cost incurred to achieve the desired outcome in the surgery arm may be found to be lower than that for the usual care arm. In this situation, hip replacement surgery is said to be more cost effective. These findings may then be used as a basis for policy change from skin traction to hip replacement surgery for such patients.

On the other hand, if it is found that surgery costs more to get to the desired outcome, then it is said not to be cost effective. This does not mean however, that the intervention is not useful. Though it costs more in monetary terms, it may afford some advantage over the usual care arm. In the example above, some patients may prefer to incur the extra cost to get the same outcome because they favour early ambulation to enable them to resume their activities of daily living earlier. For some patients, the 12 weeks of hospitalisation may be unacceptable based on their social or professional pressures and may for that reason opt for this intervention.

However, if offering the surgery comes at a great surgical risk of death or complications and is still found to cost more, then it is said not to be cost effective and also to be harmful. It may form the basis for policy against that form of intervention.

Mortality benefit may also be considered. In the example above, if it is found that the surgery arm has a mortality half that of the skin traction arm, but costs one and a half times more, the extra cost incurred per life saved is noted. If this extra cost incurred to save a life is found to be affordable, it may form a basis of adaptation of the intervention as the new standard of care. If on the other hand, it is found that an extra cost is incurred from the intervention offers no mortality benefit, it is then said to be a non cost effective form of intervention.

3.0: JUSTIFICATION OF THE STUDY:

TBM is an important cause of morbidity and mortality among HIV sero-positive patients. In our country Kenya, the high prevalence of TB translates to a high rate of clinical TBM, especially among HIV infected persons.

Diagnosis of TBM is difficult to establish. At K.N.H, this is dependent on the rare incidence of a positive Ziehl-Neelsen stain on C.S.F or evidence of TB elsewhere. Patients who have none of these will have a trial of conventional antibiotics for 14 days or so, prior to trial of therapy for TBM. This results in delay in the commencement of therapy, with resultant negative effects on morbidity, post meningitic complications and mortality.

C.S.F BACTEC- MGIT TB culture is currently the most sensitive and specific method of diagnosing TBM, requiring a short duration of time. [21, 22] [38] This however, has not been established as standard of care and comes at an added expense. MGIT C.S.F cultures done early would yield very useful information and offer both the clinician and patient an early opportunity to diagnose TBM and therefore potentially avoid or reduce mortality. This would result in a reduction of associated complications, with resultant reduction in cost to the patient, their family, the institution and to the nation on the larger scale.

Despite the fact that BACTEC MGIT cultures are costly, they can conceivably lead to a reduction of much of the cost incurred in caring for patients who would otherwise have languished in the wards while under conventional antibiotic therapy for the usual 14 day period before therapy for TBM is commenced.

4.0: RESEARCH QUESTIONS:

Is it possible to show a difference in outcome from an early diagnosis of TBM by BACTEC MGIT culture, which would justify the additional cost incurred in carrying out the investigation?

5.0: OBJECTIVES:

5.1: Broad Objective:

To determine the clinical utility and cost effectiveness of early C.S.F TB BACTEC cultures among HIV patients presenting with features of meningoencephalitis at K.N.H.

5.2: Specific Objectives:

1. To determine the proportion of CSF BACTEC MGIT TB culture positive TBM in HIV patients presenting with meningo-encephalitis.
2. To determine outcome with regards to morbidity, mortality, duration of hospital stay in the BACTEC MGIT positive arm.
3. To determine outcome with regards to morbidity, mortality, hospital stay in the non BACTEC MGIT arm patients who receive anti- TB therapy.
4. To assess the cost effectiveness of an early CSF BACTEC MGIT culture in HIV positive patients presenting with features of meningo-encephalitis.
5. To co-relate culture positivity with markers of TBM severity, such as M.R.C stage and CD4 count.

6.0: METHODOLOGY:

6.1: Study Design:

A prospective, hospital based follow up comparative two armed clinical trial

6.2: Site:

Medical wards of the Kenyatta National Hospital. A national teaching and referral hospital, in Nairobi Kenya.

6.3: Study Population:

Prospective patients admitted to the K.N.H adult medical wards during the study period with features of meningoencephalitis, who tested positive for HIV, had no contraindication to lumbar puncture, and for whom consent for inclusion was obtained.

6.4: Sampling Technique:

All consecutive patients admitted to the K.N.H medical wards who met the inclusion criteria were included. Included patients were assigned randomly into either the usual care or BACTEC arm of the study on a 1:1 and a 2:1 basis.

6.5: Sample Size:

The sample size was calculated to asses for an expected decrease in mortality by 50 percent, a result of early intervention in the BACTEC culture arm

The following formula was applied:

$$n = \frac{Z_\alpha \sqrt{\pi_o(1-\pi_o)} - Z_B \sqrt{\pi_1(1-\pi_1)}}{\pi_o - \pi_1}$$

Where:

- n is the number of subjects for the sample.
- $Z\alpha$ reflects the 1-α point and is 1.96.
- Z_β reflects the power of the study to pick a difference in mortality with a 0.84 precision. It is therefore 1-β= - 0.84.
- π_o is the existing mortality rate = 47%
- π_1 is the mortality rate expected in the early BACTEC group, by a 50 percent reduction in mortality, and is 23.5%.

Substituting the above values gives a sample size of 43 patients with a positive BACTEC result and 43 patients in the usual care arm with clinical improvement on anti-TB therapy. Using an estimate prevalence of 25%, about 160 patients would need to be recruited in the BACTEC arm to obtain the desired sample size of 43 culture positive TBM.

6.6: Case Definition and Patient Selection:

6.6.1: Inclusion criteria:

All in-patients who satisfied the following criteria were included:

1. Above the age of 13yrs.

2. Features of meningoencephalitis or an admitting diagnosis of meningitis based on any 2 of :
    a) Headache
    b) Neck stiffness
    c) Altered mental status described as confusion, increased somnolence or a change from the patients usual mental functional state.
3. HIV status positive.
4. Written consent from the patient or consent from the next of kin where the patient was unable to give informed consent.

6.6.2: Exclusion criteria:

1. Contraindication to lumbar puncture:
    a) Presence of focal neurological signs.
    b) Papilloedema on fundoscopy.
    c) a) and or b) above without a cranial CT scan, to exclude raised intracranial pressure.
    d) Infection of tissues overlying the lumbar spine.
2. Patients on treatment for tuberculosis at the time of this admission.

6.7: Screening and Recruitment:

The principal investigator (PI) reviewed admissions every morning for those who had been admitted with a diagnosis of meningitis or meningoencephalitis.

A screening profoma was used to obtain demographic data from patients admitted with this diagnosis. It included the age, gender, marital status, presence or absence of lateralising signs and papilloedema.

Pre test counseling for HIV was done by trained HIV counselors. A sample of the pre test counseling form is in appendix 4 at the end of this dissertation. An HIV rapid diagnostic test was performed at the bed side, for the patients who gave consent to be tested. Post test counseling was then done.

Patients who tested positive for HIV were assessed for contraindications to lumbar puncture. Those who had no contraindications received consent explanation for inclusion into the study. Patients who gave consent were recruited and randomized into either the usual care or BACTEC. This was done on a 1:1 basis for the first 40% of patients. At this point, an interim analysis was done. It was observed that the rate of positive BACTEC cultures was 10%, which was less that half of the estimated 25% at sample size calculation. It was then projected that to obtain the calculated sample size of 43 culture positive patients for the BATCEC arm, the usual care arm would have a much larger number of patients. In consultation with my supervisors, it was decided to double the randomization to 2:1, BACTEC: Usual Care for the next 60%.

After recruiting 89 patients in the BACTEC arm, lightly over half of the postulated 160 patients, the number of positive culture TBM patients was 14. It was projected that with this actual prevalence of 10% culture positive TBM, it at least 430 patients would need to be included to obtain 43 positive cultures. A cost effectiveness analysis was carried out at this stage, which showed that the outcome was similar between the two arms, with no cost advantage in the BACTEC arm. The decision was them made to terminate the study at this point, with the advice of my supervisors.

6.9: Clinical Methods:

A study profoma was used to record further data on patients included into the study. Each patient's clinical stage of T.B.M as per the M.T.B staging criteria was noted. They were graded by M.R.C score as stage I, II, III of TBM and their Barthel's index noted at recruitment

A lumbar puncture was performed on all included patients, under aseptic technique. The skin was prepped with 1% Povidone iodine. A total of 6 ml of CSF was obtained. The appearance of CSF was noted as either clear or not clear. The CSF samples were stood for at least ten minutes and presence or absence of a fibrin clot noted.

Those in the BACTEC arm had C.S.F BACTEC culture in addition to the usual laboratory workup at K.N.H. This usual workup consisted of C.S.F analysis by India ink and gram stains and bacterial culture. Biochemical analysis of C.S.F was also done for glucose and protein levels.

The usual care arm patients underwent usual evaluation and care, but did not have a BACTEC MGIT culture done on C.S.F. Patients in both arms were allowed to undergo the usual hospital care of antibacterial or other therapy as their clinician deemed necessary. Once a positive BACTEC culture was obtained, the PI informed the clinician in charge of the patient. Both groups were followed up for outcome, over a period of 4 weeks in-hospital stay or until discharge or death, whichever was sooner.

6.10: Laboratory Methods:

CSF obtained was handled as follows:

6.10.1: Microbiology

One milliliter of CSF was collected in a sterile bijou bottle for gram stain, India ink and aerobic bacterial culture, at routine K.N.H labs. A cell count was done using the standard Neuber chamber. CSF was then inoculated onto both blood and chocolate agar plates, for 24hrs. Remaining CSF was spun at 3000 rpm for 3 minutes and the sediment obtained stained with both India ink and gram stains.

6.10.2: Biochemistry.

Four ml of CSF was put into a non sterile fluorinated vacutainer and submitted to the routine biochemistry laboratory for protein and glucose analysis. Glucose analysis was done using the glucose oxidase colorimetric method with the random access clinical chemistry analyzer, RA 1000.

CSF protein levels were determined by the trichloroacetic acid micro protein method.

6.10.3: BACTEC cultures:

4ml of CSF was collected in a sterile bijou bottle and submitted to the Nairobi Hospital laboratory, where the cultures were carried out. The BACTEC MGIT 960 method was used.

Samples were handled in a microbiology safety cabinet SC-R re-circulating class II.

1. Decontamination:

   The Petroff method was used. Sterile 4% sodium Hydroxide (pH 6.8) was used as the sterile buffer. It was mixed with the specimen, volume for volume and stood for 15 minutes at room temperature in a 50ml sterile falcon tube.

2. Centrifuge

   The mixture in 1 above was then centrifuged at 3000rpm for 15minutes at $10^{o}C$, using an Epedorff centrifuge 5810R.

3. After centrifuge, the supernatant was decanted and 0.5ml of sterile phosphate buffer added. This was then vortexed at 2500 RPM for 10 seconds.

4. A slide was prepared and stained for A.A.F.B from the sediment.

5. Of the sample so prepared, 0.5ml was inoculated into a MGIT tube and 7ml of Middlebrook 7H9 broth base added, with 0.8ML PANTA and incubated at $37^{O}C$. The specimens were read on daily basis, starting at 48 hours.

6. Positive cultures: Tubes that yielded a positive culture were further handled as follows.

Subculture onto blood agar plates was done and read at 48 hours. Any positive result was noted.

A ZN stain was also carried out. Tubes that yielded a negative bacterial subculture result and a positive ZN stain were confirmed as M.T.B or Mycobacterium other than TB.

Those that yielded both a positive ZN and bacterial culture were considered as dual infection. Those that had a negative ZN stain but a positive bacterial sub culture were considered to have had contamination.

Mycobacteria were classified as Mycobacterium Tuberculosis or MOT based on the appearance on ZN staining.

Other laboratory tests:

CD4 counts were done using the BD FACS CALIBUR analyzer.

6.11: Patient Follow-Up:

Patients were followed up for a period of 4 weeks of hospital stay or until death or discharge whichever was sooner. This was done by daily updates from the respective wards and was accomplished with the help of a study assistant.

The following outcome variables were noted:

1. Definite TBM: BACTEC culture positive patients.
2. Probable TBM: patient commenced on anti-TB therapy on empirical basis.
3. Non TBM: patients who are BACTEC culture negative or in the usual care arm who improved on therapy other than for TB.
4. Time to commencement of anti-TB therapy
5. Time to death.
6. Average duration of hospitalization for discharged patients.

6.12: Data Analysis:

Data was entered into a data entry sheet. It was then cleaned and verified to ensure that quality was maintained. Statistical analysis was performed using Statistical Package for Social Sciences version 11.2 software, for windows. Analysis involved descriptive statistics such as mean, median and standard deviation for continuous variables such as age, duration of symptoms, time to anti-TB therapy, duration of hospital stay and time to death. Frequency distribution was used for categoric variables such as gender, and CSF culture results and CD4 counts less than or greater than 200. Proportions were calculated for each for the outcome variables in each of the two groups. Comparison was made between the two.

Data has been presented in tables, graphs, pie charts.

6.12.1: Cost effectiveness analysis technique:

A very elementary form of C.E.A was used for this study. This compared the cost per discharged patients in the usual care on one hand against that of discharged patients in the BACTEC arm, on the other hand. The measure of cost per hospitalization day that was used is the sum of daily bed charges, nursing and doctors' charges.

a) Morbidity benefit:

This was assessed by comparing the cost of hospitalization for the discharged patients in the two groups:

$$\frac{(N_1 \times C)H + (\text{cost of BACTEC})N_1}{\acute{\eta}_1} \quad : \quad \frac{(N_2 \times C)H}{\acute{\eta}_2}$$

Where:

N_1 = number in BACTEC arm.

N_2 = number in usual care arm

$\acute{\eta}_1$ = total discharged in BACTEC arm.

$\acute{\eta}_2$ = total discharged in usual care arm

C = daily hospital charge.

H = average number of hospitalization days in that arm.

The proportion on the left side of the comparison signifies the cost per discharged patient on the BACTEC arm. The numerator is inclusive of the total hospitalization cost and total BACTEC cost. The denominator is the number of patients who improved to discharge on anti TB treatment in that arm.

The proportion on the right signifies the total cost of usual care reflected per discharged patient. It had been postulated that doing an early CSF BACTEC culture would result in an earlier time to starting anti-TB treatment with a resulting larger proportion of discharged patients as well as a shorter duration of hospitalization. This would reflect as larger denominator in that arm and a shorter average hospitalization stay. This, it had been anticipated, would result in a lower figure for the BACTEC proportion, despite the

extra cost incurred to carry out the investigation. A ratio <1 would suggest that despite the extra cost incurred, it would be more cost effective to employ BACTEC for these patients. A ration of 1:1 suggests that the two methods cost the same whereas a ratio >1 suggests that it is not cost effective to carry out the investigation.

b) Mortality benefit:

A comparison was to be made between morality outcomes in the two groups. The cost per life saved was evaluated as follows:

$$\frac{\text{Total cost of BACTEC arm} - \text{total cost for usual care arm}}{\text{Mortality in usual care} - \text{mortality in BACTEC arm}}$$

It had been anticipated that an early BACTEC would result in an early time to treatment therefore reduction in mortality in the BACTEC arm relative to the Usual care arm. The formula above would be used to calculate the extra cost per extra life saved, if the BACTEC was found not to be cost effective. If no difference in mortality was observed, then it would be concluded that the test did not offer any mortality advantage despite the extra cost incurred. If the difference in mortality favored usual care, then it would be considered cost ineffective to invest in BACTEC.

6.13: Ethical Considerations:

The study was conducted after approval by the Department of Internal Medicine, University of Nairobi and the Kenyatta National Hospital Scientific and Ethical Review committee.

Pre test counseling for HIV testing was done for patients admitted with a diagnosis of meningitis/ meningoencephalitis. Those who consented to testing had post test counseling to inform them of their HIV status, as well as advice them on any lifestyle changes that would improve their survival if positive, or prevent infection if negative.

Patients who tested HIV positive had a physical examination to exclude contraindications to a lumbar puncture. Those without such contraindications received a written explanation of what the study entailed and its potential benefits to them. and other patients with meningitis and HIV, from the principal investigator. In the event that a patient was not in a position to give consent, their next of kin received the consent explanation on their behalf.

Patients or their next of kin where patient had altered mental status were informed that the project involved research. They were told the purpose of the research and received an explanation of the study process, with an explanation of the tests to be done in lay terms.

Potential benefits and harms were explained to them. They were assured that their participation in the study would be voluntary and that they were free to decline to participate or to withdraw from the study at any point, without any penalty. They were assured that confidentiality would be strictly maintained and that all data obtained would be securely stored.
Following this, an offer to answer questions or to provide further, information was made to them. In the event of a favorable response, the patient was then requested to sign an informed consent form.

7.0: RESULTS.

7.1: RECRUITMENT:
Between January and April of 2007. 219 consecutive patients were screened.
77 patients were excluded for the following reasons: 2(0.8%) patients declined consent for inclusion into the study, 15(19.4%) were HIV negative, 50(64%) patients had contraindication to a lumbar puncture and 10 were on anti-TB treatment. These patients did not differ significantly in demographics or in meningo-encephalitis features from the patients included in the study.

A total of 142 patients met inclusion criteria. Of these, 89 were allocated to the BACTEC arm and 53 to the usual care arm.

7.2: DEMOGRAPHIC DATA

The mean age of all patients included into the study was 36.9 years ± 9.57SD, range between 13 and 62 years with a median of 36.5yrs. The mean age of patients in the BACTEC arm was 36.87 ± 10.3SD, with a median of 36yrs. In the usual care arm, the mean age was 37.53 ±8.2SD with a range between 13 and 55 years and a median of 38yrs. There was no statistically significant difference in age between the two groups, p = 0.68. This is summarized in table 2 below.

Age	Mean	STD	Median	Minimum	Maximum
BACTEC (n= 89)	36.87	10.287	36	13	62
Usual care (n=53)	37.53	8.27	38	13	55
Total n= 142	36.96	9.577	36.5	13	62

P=0.68

Table 2: Age Distribution of Included Patients.

Of the 142 patients, 68 (49%) were male. In the BACTEC arm, they were 43(48.3%) while in the usual care arm they were 25(47.1%). There was no statistically significant difference between the two groups, with a p value of 0.936.

Gender	Randomization		Total
	BACTEC	Usual Care	
Male	43(63.2%)	25(36.8%)	68
Female	46(63.9%)	26(36.1%)	72
Total	89	51	140

X^2 =0.006, df = 1, p=0.936

Table 3: Table Of Gender Distribution For Included Patients..

7.3: CLINICAL CHARACTERISTICS

7.3.1: M.R.C stage.

A large proportion of patients 82(57.7%) were in M.R.C stage II, 22(15%) were in stage I while 35(24.6%) were in stage III. There was no statistically significant difference in M.R.C staging between the 2 groups.

M.R.C stage	Randomization		Total	P value
	BACTEC	Usual Care		
I	19(21.34%)	6(11.30%)	25(15.5%)	o.02
II	49(55.06%)	33(62.23%)	82(57.7%)	0.20
III	21(23.60%)	14(26.41%)	35(24.6%)	0.56
Total	89	50	142	

χ^2=5.662   df=2   overall p value=0.059

Table 4: M.R.C staging of severity of meningoencephalitis.

7.32 Barthel's index.3.2: Barthel's index.

At admission, the Barthel's index was less than 6 in 19(19.4%) of patients scored. 62(63.3%) had a score between 6 and 12 while 17(17.3%) had a score above 12. there was no statistically significant difference in Barthel's index at admission between the two groups, as shown in the table below.

Barthel's index	BACTEC N (%)	Usual care N (%)	All	P value
>12	14 (21.5%)	3 (9.1%)	19(19%)	0.12
6-12	40 (61.5%)	22 (66.7%)	62(63%)	0.622
<6	11 (16.9%)	8 (24.2%)	17(17%)	0.38

The p = 0.266

Table 5: Table Of Barthel's Index At Admission.

Majority of discharged patients had a Barthel's score >12. in the BACTEC arm, they were 33(78%) of the discharged patients, while in the usual care arm they were 19(70.4%). There was no statistically significant difference between the two.

Barthel's index	BACTEC N (%)	Usual care N (%)	All	P value
>12	33 (78.6)	19 (70.4)	52(75.4)	0.44
6-12	7 (16.7)	6 (22.2)	13(18.8)	0.53
<6	2 (04.8)	2 (07.4)	4(5.8)	0.60

Table 6: Table Of Barthel's Index At Discharge.

7.4: LABORATORY CHARECTERISTICS

7.4.1 CD4 counts:

CD4 T Lymphocyte counts were available for 109(76.7%) of the patients. They were not obtained for 33 patients during their hospitalization. Only 4 patients, all of whom were in the BACTEC arm, had CD4 counts >200. All other patients had their CD4 counts below 200.

CD4 Count	Randomization		Total	p value
	BACTEC	Usual Care		
<200	66(94.3%)	39(100%)	105	0.29
>200	4(06.7%)	0(0.0%)	4	-
Total	70	39	109	0.29

χ^2=2.313   df=1   p value=0.29

Table 7: CD4 Counts In the Study Population.

7.4.2: Cerebrospinal fluid

Gross CSF appearance:

In 66(46.5%), the CSF appearance was noted to be cloudy. In 65(45.8%), it was not cloudy while in 11(7.7%), no note was made. In the BACTEC arm, 50(75.8%) had a cloudy CSF appearance while in the usual care arm; there were 16(24.2%). There was a statistically significant difference between the 2 with this regard, p=0.05. The table below summarizes these details.

CSF Appearance cloudy	Randomization		Total
	BACTEC	Usual Care	
Yes	50(56.2%)	16(30.0%)	66
No	39(43.8%)	26(49.0%)	65
Not noted:		11 (21.0%)	11
Total	89	42	142

χ^2=3.73   df=1   p value=0.05

Table 8: Table of Gross appearance of CSF.

CSF Chemistry:

For the purposes of this study, CSF protein was categorized as either <0.45, which is normal, or > 0.45 which is elevated. CSF protein was >0.45g/l in 45(31.7%) of patients, in the hole study population. In the BACTEC arm, 54(65.9%) had their CSF protein <0.45, while 28(34.1%) had their CSF protein >0.45g/dl. In the usual care arm, 29(64.4%) had protein < 0.45. CSF biochemistry results could not be traced from the routine laboratory for14 (9.9%) of patients.

CSF Protein	Randomization		Total
	BACTEC	Usual Care	
<0.45	54 (60.7%)	29 (54.7%)	83 (58.4%)
>0.45	28 (31.5%)	16 (30.2%)	44 (31.0%)
Missing	7 (07.8%)	8 (15.1%)	15 (10.6%)
Total	89	53	142

χ^2=0.025   df=1   p value=0.87

Table 9:Table of CSF protein

The CSF glucose was <2.2 mM/l in 77(61.1%) and >2.2mM/l in 49(38.9%). Results could not be traced from the laboratory for 16(10.6%).

CSF Glucose	Randomization		Total
	BACTEC	Usual Care	
<2.2	51(66.2%)	26(33.8%)	77
>2.2	30(61.2%)	19(38.8%)	49
Total	81	45	126

χ^2=0.327   df=1   p value=0.567

Table 10: Table of CSF Glucose

The C.S.F gram stain was positive in 12(9.7%) of the 124 patients for whom a bacteriology result was obtained. These were gram positive suggestive of streptococci. Microscopy results could not be traced for 12.7% of patients.

The BACTEC culture results were positive in 9(10.1%) at 21 days, 14(15.7%) at 8 weeks respectively. Of the 9 patients with a positive culture, results were obtained within 7 days for 1(11.9%) while the other 8(88.8%) had results between day 7 and 21, with an average of 14 days. These details are summarized in the graph below.
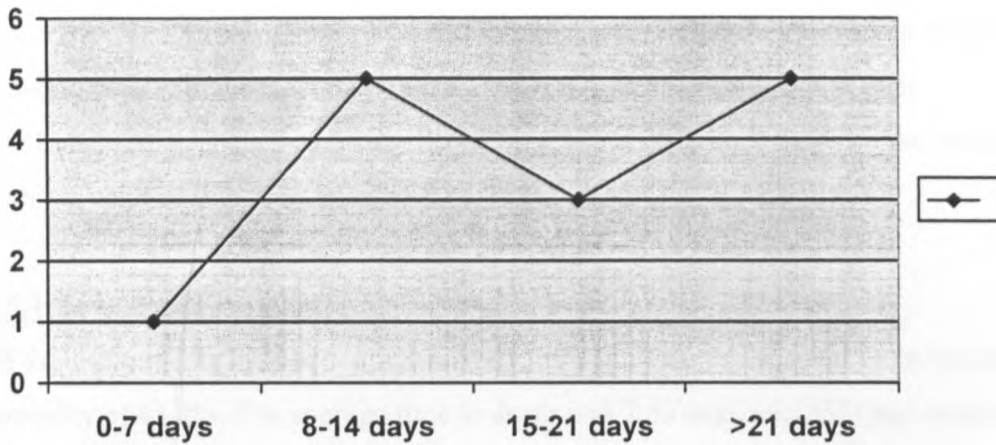
Figure 3: Graph of time to culture positive results.

Y axis represents number of patients.

7.5: OUTCOME VARIABLES:

7.5.1: TBM Diagnostic categories:

Definite TBM was found in 14(15.7%) patients, 96%C.I. (15.5-15.9). Another 44(30.9%) had probable TBM, based on a clinical improvement on commencement of anti TBM therapy. In the BACTEC arm, they were 25(28.7.3%), while in the usual care arm, they were 19(35.8%). No statistically significant difference was found between the two groups, p=0.515. non TBM patients were 31(21.8%). In the BACTEC arm, they were 21(23.5%) while in the usual care arm they were 10(30.9%).

7.5.2: Time to anti-TB therapy

The average time to anti-TB therapy was 5.51 ±4.49SD, range 1-28 days. In the BACTEC arm, this was 4.7days, ±4.49SD, compared to 6.8 ±5.5SD days in the usual care arm, p=0.083.

7.5.3: Duration of hospital stay for discharged patients:

The average duration of hospital stay in this study population, for the discharged patients was found to be 11.2 ±4.9SD, range 1-22 days.

In the BACTEC group, the mean duration of hospitalization for discharged patients was found to be 10.56±4.4SD, while that for the usual care arm was found to be 14.48±8.262SD. There was a statistically significant difference between the two groups with a p value at 0.029, in favor of BACTEC.

7.5.4: In hospital mortality:

Of the 142 patients included into this study, 65 died. This represented an in hospital mortality of 45.8%. The average time to death was 7.53 days ±6.13SD and ranged between 1 and 28 days. In the BACTEC arm this was 10.56±4.49SD, while in the usual care arm, it was 6.93±5.198SD. There was no statistically significant difference, in the average time to death for patients in the two groups, p=0.108.
In the BACTEC arm, 41(46%) died. In the usual care arm, 22(41.5%) died. There was no statistically significant difference in the mortality between the two groups, p = 0.225.

7.5.5: BACTEC positivity and markers of TBM severity:

The average age of patients with a positive culture was 38.43±10.09 SD, mean 38.0, range 24-56 years. One patient was in M.R.C class I while 7(50%), were in class II and 6(42.9%) were in class III.

All 14 of the culture positive patients had CD4 counts below 200. Out of these, 12(85.7%) died, all within 7 days of admission. Numbers were too small to allow for calculation of correlation coefficients, to correlate culture positivity and markers of disease severity. .

7.5.6: Cost effectiveness analysis:

It had been postulated that doing an early CSF BACTEC culture would led to earlier diagnosis and treatment of patients therefore reduction in duration of hospital stay and an increase the proportion of patients that would be discharged, forming the basis for a cost effectiveness analysis.

This, it was predicted, would be demonstrated using the formula below:

$$\frac{(N_1 XC)H + (C_B XN_1)}{\eta_1} \quad : \quad \frac{(N_2 XC)H}{\eta_2}$$

Where:

N_1 = number in BACTEC arm.

N_2 = number in usual care arm

$\acute{\eta}_1$ =total discharged in BACTEC arm.

$\acute{\eta}_2$= total discharged in usual care arm

C= daily hospital charge.

H= average number of hospitalization days in that arm.

Substituting these values,

$$\frac{(89 \times 1000)11 + (1200 \times 89)}{27} \quad : \quad \frac{(53 \times 1000)14.0}{19}$$

= 40214 : 39052

= 1.03

Employing the formula stated in 6.12 above, it was found that the cost effectiveness ratio of BACTEC to Usual Care was 1.03:1. It cost 3% more per discharged patient in the BACTEC arm than in the usual care arm. It was therefore not cost effective to carry out the cultures for the purpose of early diagnosis of TBM.

7.5.7: Mortality benefit:

There was no observed difference in mortality between the two arms.

A mortality benefit analysis could therefore not be calculated.

8.0: DISCUSSION.

Meningitis is a condition that is seen fairly commonly at KNH. This is especially so in the background of HIV. During the three month study period, a total of 219 patients were admitted with this clinical diagnosis and were screened. 35% of these had contra indications to a Lumbar puncture based on focal neurological signs or papilloedema, both markers of disease severity. This was not designed as a prevalence study and was therefore not powered to compare demographics with other studies. However, the mean age of included patients was 36.9 years. This was similar to that found by Hooker et al in the same institution as well as other investigators elsewhere.[12, 13, 16, 25, 41-43]

Of the included patients, 70(49%) of patients were male. This was similar to findings by Hooker et al, at the same institution.[13] but differed, though from findings by investigators in other places, where males have been found to form a larger proportion of patients with TBM. [12, 42, 44] Since numbers were small, inference could not be made as to the possible reasons for this difference.

More than half (57%) of patients in this study had disease of moderate severity as evidenced by M.R.C stage II. The Barthel's index at admission was also reflective of moderately severe disease, with 63% of patients having a score between 6 and 12, meaning that they were able to carry out their activities of daily living while relying to a large extent on assistance from others. This understandably is to be expected as a similar percentage of patients were found to be in M.R.C stage II. Thwaites et al, who found 47.9% of the 96 HIV positive patients with meningitis in their study to be in M.R.C stage II. [11] Other investigator have also had similar findings [12, 13, 42]

The pro-dromal symptoms of TBM that define M.R.C stage I are very non specific. Patients tend to self medicate or seek other forms of therapy prior to seeking medical advice. As a result, they tend to present with more advancing disease. It is not surprising, therefore, that most patients present to our institution with clinical signs of M.R.C stage II disease.

CD4 cell counts were done on 109 patients, during the course of their hospitalization. Majority of these were severely immunosuppressed, with counts below 200. All of the BACTEC culture positive patients fell in this category. Meningoencephalitis is a severe form of illness often occurring in the setting of severe immunosuppression. This finding was therefore to be expected and is similar to that of Thwaites et al, who found an average CD4 count of 67×10^9 cells/ml in their study on the influence of HIV on the clinical presentation, response to therapy and outcome in adults with HIV. In their study, they did CD4 counts in 79 HIV positive patients with either definite probable or possible TBM, and found a range between 7-694 $\times 10^6$ cells per ml. [11]

In 45.5% patients, the CSF appeared cloudy. However, on biochemical analysis, 31% had a CSF protein >0.45g/l. Majority of patients had protein < 0.45g/l. This is in contrast to findings by other investigators who have found an elevated CSF protein in most patients. [11-13, 45]

The CSF glucose was low in majority of the patients. This was consistent with findings by other investigators. Katrak et al found an average CSF glucose of between 0.25 and 1.0mM/l. other investigators such as Berenguer, Hooker, Thwaites have also found low glucose levels in patients with proven or suspect TBM. [11, 12, 13, 41-43] Microscopy was positive in only 9.7%. There was no co-infection of TBM and other microorganisms in this study.

BACTEC positivity was 15.7% at 8 weeks. This differed from the findings by Hooker et al, also found 35.3% cultures positive for TBM. This difference may be explained by the fact that in their study, they included patients with a high clinical probability of TBM, whereas in this study, all patients with HIV and a clinical syndrome of meningitis have been included, in whom it is likely that other etiological agents would be responsible for the clinical syndrome of meningoencephalitis .[13]

The average time to BACTEC positive result was 12 days. In one patient, the culture result was obtained on day, 6. Unfortunately, the patient had died on day 2 post

admission. Five patients had a positive culture result obtained after day 21, which for the purposes of this study was not an early diagnosis,

Definite TBM was found in 15% of patients in the BACTEC arm. Silber et al reported similar findings of 9 out of 57 patients with HIV and meningitis in South Africa.[16] This prevalence was however, much lower than that found by Hooker et al, at KNH, who found a prevalence of 35% of culture positive TBM.[13] This difference may be accounted for by the fact that they selected patients with a high clinical probability of TBM, whereas in this study, we have included all patients regardless of their clinical probability for or against TBM. In Hooker's study, patients with focal neurological signs were included if cranial CT scans showed that there was no contraindication to a lumbar puncture. In our study, we excluded these patients because it would normally require a day or two to get a cranial CT scan, which would not fit the definition for early CSF culture.

The average time to a positive culture result was 12 days, with the shortest being 6 days. 5 patients had their culture results beyond day 21. In their studies, Hanna et al and Somskovi et al found an average time to culture result to be 10.3 and 14 days respectively, comparable to findings in our study.[21, 22]

About a third of patients were thought to have probable TBM. These were defined as patients who had empirical therapy for TBM and improved. There was no statistically significant difference in the proportions of patients with probable TBM between the two groups. Since in the two arms the decision to start anti-TB therapy was empirical, this was to be expected. Given the severity of this illness, it may be said that it was a rational decision to commence treatment for TBM in these patients despite evidence at the outset.

Patients admitted with a diagnosis of meningitis that improved and were discharged on therapy other than that for TBM were classified as non TBM and formed 21.8% of the study population.

There was no statistically significant difference in the time to anti-TB therapy between the two arms. In both, the decision to commence anti-TB therapy was made on empirical basis. Some clinicians commenced anti-TB therapy based on evidence elsewhere in the body, such as on chest radiography. Most. however, commenced this treatment based on the clinical severity of illness. Patients admitted in comma were more likely to receive anti-TB treatment earlier into their hospitalization. The general sentiments of clinicians under whose care these patients were was that withholding anti TB treatment until the diagnosis was established may deny the very ill patient a chance of survival. Doing a CSF BACTEC culture did not influence the time to clinical decision to commence therapy for any of the patients. This may be considered a rational decision, since TBM is a severe illness and often does not allow much time for laboratory investigation to be carried out. Both of the patients who had a positive CSF culture for TB and survived both had treatment commenced empirically. Their CSF culture results were obtained after they had been discharged home on treatment. All the other patients with positive cultures for TB died before their results had been obtained. The BACTEC culture therefore did not reduce time to commencement of anti-TB therapy in any of the patients who had a positive result. On the other hand, there is a potential for indiscriminate use of anti-TB treatment. The probability of TBM should be borne into consideration based on evidence of TB elsewhere in the body, to minimize misuse of these drugs. This is argument is strengthened by the fact that we observed a prevalence of culture positive TBM of only 15%.

The average duration of hospitalization was 11.2 days, in the whole study population. There was a statistically significant difference in duration of hospitalization between the two groups, in favor of the BACTEC arm; 10.56 vs. 14.48 p=0.029.

This difference could not be attributed to the fact that a BACTEC culture had been done, as the culture result did not influence time to clinical decision making. It may therefore suggest a confounding factor. The baseline characteristics were similar between the two groups, which would be expected to balance out all confounders between the two groups. It therefore is likely that this was a chance occurrence.

Mortality in this study was 45.8%. Among the 41 patients in the BACTEC arm who died, 12(31%) had definite TBM by culture. Therefore, 69% of these deaths could be attributed to another cause other than TBM. Mortality among the patients with definite TBM it was found to be 85%, all within the first 7 days of admission. It is notable that all patients who died of definite TBM were in MRC stage II and III. In the BACTEC arm, there was 46% mortality, 13% BACTEC culture positive. Since the sensitivity of BACTEC is about 95%, this suggests that 33% of mortality was caused by an agent other than TB.

The high and early mortality observed in the patients in this study may be partially explained by the fact that these were severely immuno-suppressed patients, as evidenced by the CD4 counts. Due to this immunosuppression, they are likely to have had other opportunistic infections that would have contributed to their mortality.

All patients with a positive BACTEC culture had their CD4 counts below 200. This is a marker of severe immunosuppression.[5] The average age of culture positive patients was 38.46yrs, ±10.09SD, not differing from that of the whole study population.

Of the definite TBM patients who survived, one was in MRC stage I while the other was in stage II. All the rest were in stage 2 and 3, one of whom survived while the rest died. This is not surprising since it is established that Stage III disease is associated with high mortality especially in the presence of coma or convulsions.[2,3,25] It may be argued that perhaps had patients presented in earlier stage of disease, the mortality would have been lower. However, numbers are too small to lead to solid conclusions. Correlation coefficients could not be calculated since numbers were small.

Carrying out a BACTEC culture translated to a X1.03 higher cost per patient discharged in the BACTEC than usual care arm. Doing this culture did not influence time to clinical decision making and thus had no influence on clinical outcome as had been hoped. It was therefore not cost effective to carry out BACTEC CSF cultures in HIV positive patients with meningoencephalitis. The small numbers in this study preclude solid

conclusion. Had patients presented in stage one, there may have been a clear advantage in carrying out the CSF cultures at admission. That having been stated, though an extra cost was incurred that did not translate to improved clinical outcome, it is useful to note that patients who had the culture done had an opportunity to have proof of diagnosis for the disease. Though this did not reflect as an improvement in their prognosis, it offers a benefit to the patient and the clinician which cannot be measured in monetary terms. The C.E.A suggests that BACTEC cultures should not be employed with an aim of having a gain in cost, but this non quantifiable benefit may outweigh the disadvantage of the extra cost. This means that although the BACTEC method may not be adopted as standard of care, it should not be discarded altogether despite a negative result in the C.E.A.

There was no mortality benefit demonstrated.

9.0 CONCLUSION:

Meningo-encephalitis has a very high mortality rate, at almost 50%. This is even higher, in those with tuberculous meningitis, at 85%. Among the HIV positive patients with meningoencephalitis, the prevalence of TBM by BACTEC culture was found to be 15.7%. There is no statistically significant difference in time to diagnosis, duration of hospital stay, mortality and morbidity between the BACTEC and usual care arms. It is therefore not cost effective to perform a BACTEC culture in these patients, for the purpose of early diagnosis and treatment of TBM. The presently high cost of BACTEC cultures does not justify its routine use in HIV positive patients with meningoencephalitis.

Further, the findings of this study show that 15% of patients presenting with a clinical syndrome of meningoencephalitis have TBM, within a sensitivity of 95%. This suggests that the remaining 85% of patients have alternative causes of their disease. Majority of patients presented in late stages of disease, which to a large extent influenced the outcome.

10.0: RECOMMENDATIONS:

1. A larger study of a similar nature but targeting patients in earlier stages of TBM be carried out, to demonstrate the advantage of early BACTEC cultures in these patients.

2. Studies be carried out to seek other causes of the meningoencephalitis syndrome in patients with HIV.

3. There is a need to rationalize empirical therapy for TBM. Algorithms should be developed to guide clinical decision making based on the probability of TBM in the individual treatment, rather than ad hoc.

11.0: STUDY LIMITATIONS:

In our study, we encountered very sick patients, a number of whom were excluded because of contraindications to lumber puncture. Had these patients presented earlier, there would conceivably have been more patients with an early culture result, which would probably have influenced results in favor of BACTEC.

Part of the exclusion criteria of the study is presence of raised intracranial pressure and focal neurological signs. These are some of the sequel of TBM especially in stage II and III of illness. Had it been possible to include these patients, a higher prevalence of TBM would probably have been observed.

12.0: APPENDICES

APPENDIX I - SCREENING PROFOMA:

Study No ☐☐☐

Date of Admission ☐☐☐☐☐☐   Ward No ☐☐

Name: ....   Hospital No: ☐☐☐☐☐☐

Age (Years): ☐☐ DOB: ☐☐ ☐☐ ☐☐☐☐

Contact Details: P.O. Box........................ Tel. No: ....

DEMOGRAPHICS

1. Gender 1= Male 2=Female   ☐

2. Marital status   ☐

    1=Single   2=Married   3=Divorced   4=Widowed   5=Separated

3. Usual residence ....

4. Usual occupation   ☐   1 = self employed 2 = employed

    3 = unemployed   4 = retired   5 = training/student

5. Level of education   ☐   1 = None2 = Primary school

    3=Sec. School; 4 = Tertiary level;   5=other (specify).......................

6. Duration of symptoms: (Days)

Headache   ☐☐   Fever   ☐☐   Weight loss   ☐☐

Night sweats   ☐☐   Irritability   ☐☐

Alteration in level of consciousness   ☐☐

ELIGIBILITY

1. After pre test counseling for HIV: patient willing to have the HIV test done? 1 = YES   2 = NO   ☐

HIV Rapid result: 1= Positve 2= Negative   ☐

Focal Neurological signs: Yes=1 ; NO=2   ☐

Cranial Nerve palsies: Yes=1; No=2   ☐

If yes, state which cranial Nerve(s) ....

Papillo- edema: Yes=1; No=2   ☐

Choroid tubercles Yes=1, No=2   ☐

Contraindication to Lumbar puncture: Yes (1) NO (2)   ☐

Consent to be included into the study:

Have you understood what the study is about? Are you willing to be included in the study:

CLINICAL UTILITY AND COST EFFECTIVENESS OF C.S.F TB BACTEC CULTURES IN THE EVALUATION OF HIV SEROPOSITIVE PATIENTS PRESENTING WITH MENINGOENCEPHALITIS AT THE KENYATTA NATIONAL HOSPITAL. YES (1) NO (2)   ☐

FOR OFFICIAL USE

Recruited   1 = YES   2 = NO   ☐

Appendix II: Study Profoma:

(To be appended to screening profoma for included patients.)

1. Randomization: BACTEC arm (1) usual care (2)   ☐

2. M.R.C stage: I, II, III   ☐

3. CSF Appearance

   Cloudy YES =1; NO =2   ☐

4. Fibrin clot

   YES =1; NO =2   ☐

1. CD4 count: _____ <200=1, >200=2

2. CSF protein:_____ <0.45=1, 0.45=2

3. CSF glucose:_____ <2.2=1, >2.2=2

4. CSF Gram stain: Positive =1 Negative =2   ☐

5. CSF CELL COUNT: Neutrophils…..   Lymphocytes….

6. BACTEC culture: number of days to result: ☐☐

7. BACTEC: Positive =1; Negative =2   ☐

8. Time to commence anti TB therapy (days).   ☐☐

9. Date of admission ☐☐☐☐   Date of discharge: ☐☐☐☐

10. Barthel's index at admission ☐☐   Barthel's index at discharge ☐☐

11. Death: YES =1; NO =2   ☐   date of death ☐☐☐☐

   If yes, number of days from admission to death: ☐☐

APPENDIX 3: HIV COUNSELING FORM.

My name is _____ (counselor's name).

We shall talk a little bit about HIV.

Have you heard of HIV/AIDS? What do you understand by this?

HIV is an infection caused by what we call a virus. One might get this infection by various ways:

1. Through sex.
2. Infection passing from mother to child.
3. By blood transfusion.
4. By needle prick with a dirty needle that has been used on someone with HIV.

Infection with HIV results in slow destruction in the body's ability to fight disease. After some time, this ability is so affected that the person gets many infections and if not treated leads to death. This is when we say that the person has developed AIDS.

Have you ever had an HIV test done? (What were the results?)

It is important that we do an HIV test on you now. It will help us know how to best treat you. Knowing your HIV status also helps you plan your life better.

If the result is positive, we shall let you know and advice you on how best to prevent infection with HIV.

If the result turns out positive, we shall be able to do further tests and see how far the disease has gone. We shall then help you get the required treatment.

APPENDIX 4: CONSENT EXPLANATION.

You have been admitted to this hospital for treatment of a condition that we call meningitis. We shall need to test some fluid from your back, to see which kind of infection you are suffering from. This fluid is obtained by a process called a Lumber puncture. A special needle is used to get this fluid from the lower back. We shall give you an injection to prevent pain as we do the lumbar puncture. This is what we do for all our patients with meningitis.

This is a study being done for patients with meningitis, to specifically check for TB. In this study, a special test is done on the fluid that we get from the lumber puncture. This test will not be at an extra cost to you.

By doing it, we expect that we can identify TB infection early and so start you on the correct treatment earlier, if the result of the test is positive This will help you get better sooner and prevent an unnecessarily long stay in the ward.

For us to test you in this way, we need you to understand that this test will only be offered if you give your permission. If you do not wish to have the extra test done, we shall still offer you the treatment that we would have, had the test not been available. We are doing this research so that we can see the usefulness of this test to patients who have an illness similar to ours. We expect that if we are able to identify TB early, we will have patients needing to be in hospital for a shorter time and also that they can be discharged stronger. We also expect that we will be able to save some patients who would have lost their lives while under investigation.
The results of the test will be treated in strict confidence. You are free to agree or to decline that you should be included in this study.

Thank you.

APPENDIX 5: CONSENT FORM.

I, _____, have understood the

Explanation of this study:

"CLINICAL UTILITY AND COST EFFECTIVENESS OF CSF BACTEC CULTURES IN THE EVALUATION OF HIV SEROPOSITIVE PATIENTS PRESENTING WITH MENINGOENCEPHALTIS AT THE KENYATTA NATIONAL HOSPITAL", from Dr. Lois Wagana.

I freely choose to participate in this study and I understand that whether or not I Participate will not affect the care that I receive. I also understand that I may at any point choose to withdraw from this study.

Signed: _____

Witnessed: _____

APPENDIX 6: THE BARTHEL'S INDEX.

1. **Bowels:**
   a. Continent   2
   b. Occasional accidents   1
   c. Incontinent   0

2. **Bladder**
   a. Continent   2
   b. Occasional accidents   1
   c. Incontinent   0

3. **Feeding**
   a. Independent   2
   b. Needs some help   1
   c. Dependent.   0

4. **Grooming: face/hair/teeth/shaving:**
   a. Independent   1
   b. Needs some help   0

5. **Dressing**
   a. Independent   2
   b. Can do half   1
   c. Dependent   0

6. **Transfer**
   a. Independent   3
   b. Minimum help needed   2
   c. Major help needed (can sit)   1
   d. Unable   0

7. **Walking**
   a. Independent   3
   b. Walks with a stick   2
   c. Wheel chair dependent   1
   d. Unable   0

8. **Stairs**
   a. Independent   2
   b. Needs some help   1
   c. Dependent.   0

9. **Bathing**
   a. Independent   1
   b. Needs some help   0

Total: **18**

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