THE AETIOLOGIES, CLINICAL PRESENTATION, DIAGNOSTIC DIFFICULTIES AND OUTCOMES OF MENINGITIS AMONG HIV-POSITIVE ADULTS ADMITTED TO LIVINGSTONE HOSPITAL, PORT ELIZABETH

A mini-thesis submitted in partial fulfilment of the requirements for the degree Master of Public Health in the School of Public Health, Faculty of Community and Health, University of the Western Cape.

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DECLARATION

I declare that the work presented herein, "The aetiologies, clinical presentation, diagnostic difficulties and outcomes of meningitis among HIV-positive adults admitted to Livingstone hospital, Port Elizabeth", is original and that it has not been submitted for any degree or examination in any other university or institution for the award of a degree or certificate and that all sources of information and data used or quoted have been duly indicated and acknowledged.

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ABBREVIATIONS

ADA	Adenosine Deaminase
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ART	Antiretroviral Therapy
AST	Aspartate transaminase
AUR	Auramine stain
BM	Bacterial Meningitis
CCM	Cryptococcal Meningitis
CDC	Centres for Disease Control and Prevention
CNS	Central Nervous System
CrAg	Cryptococcal Antigen
CRP	C-Reactive Protein
CSF	Cerebrospinal Fluid
CT	Computerized Tomography
FBC	Full Blood Count
GGT	Gamma-Glutamyl Transferase
GXP	GeneXpert MTB/RIF
HIV	Human Immunodeficiency Virus

LFA	Lateral Flow Immunoassay
LP	Lumbar Puncture
MRI	Magnetic Resonance Imaging
NHLS	National Health Laboratory Service
TBM	Tuberculous Meningitis
VM	Viral Meningitis
WHO	World Health Organization

OPERATIONAL DEFINITIONS

- *Suspected meningitis*: Patient admitted with symptoms and signs suggestive of meningitis as determined by the admitting physicians.
- *Confirmed meningitis*: Patient with suspected meningitis and cerebrospinal fluid (CSF) biochemical and/or microbiology features consistent with meningitis. This included demonstration or evidence of a typical causative organism in the CSF.
- *Advanced HIV disease:* HIV disease with low CD4 counts of less than 200 cells/mL or the presence of AIDS-defining illnesses.
- *Aseptic Meningitis:* This is also described as Lymphocytic Meningitis. Clinical features for meningitis and CSF lymphocytic pleocytosis, but no pathogen is identified in the CSF.
- *Bacterial meningitis:* CSF positive for gram-positive cocci in pairs, bacterial antigen test or by isolating the causative organism bacterial culture of the CSF.
- *Cryptococcal meningitis:* CSF positive for capsulated yeast cells by India ink stain, or cryptococcal antigen by a latex-agglutination test/lateral flow immunoassay, or by a positive culture for *Cryptococcus neoformans*
- *CSF pleocytosis:* Raised white cell count in the CSF
- *Tuberculous meningitis:* CSF positive for Acid Fast Bacilli, by isolating *Mycobacterium tuberculosis* by CSF culture, by positive GeneXpert MTB/RIF or by elevated ADA of ≥ 6
- *Viral Meningitis:* CSF positive for meningitis virus screen. The virus screen done NHLS involves a multiplex PCR for the detection of viruses that can cause meningitis. The panel of viruses screened for in this multiplex PCR includes Cytomegalovirus, Epstein-Barr virus, Herpes Simplex virus type 1, Herpes Simplex virus type 2, Human Herpes virus type 6, Varicella Zoster virus; Enterovirus Panel includes Human Enterovirus and Mumps virus.

ABSTRACT

Background: Meningitis is a common opportunistic infection and an important cause of mortality among people living with HIV and AIDS globally.

Objectives: This study investigated meningitis in adults living with HIV and AIDS admitted to the medical wards of Livingstone tertiary hospital in Port Elizabeth in 2018 and determined the prevalence of its aetiological types, clinical presentations, diagnostic challenges, treatment outcomes and predictors of prognosis.

Methods: The study was a clinical records review of people living with HIV who were admitted with meningitis for the period 1st January to 31st December 2018. A data extraction tool was used to collect patients' demographic information, neurological symptoms and signs, baseline immune status and other blood workups, as well as the results of lumbar puncture. The data were analysed using the R software.

Results: A total of 122 clinical notes that met the eligibility criteria were reviewed for this study. The cerebrospinal fluid findings were normal in 22% (27/122) of cases, while 21% (25/122) had findings consistent with meningitis but no identifiable microbial aetiology. Among the 70 patients with microbiological diagnosis of meningitis, cryptococcal meningitis was the most prevalent – accounting for 54% (38/70) of the cases. Tuberculous meningitis accounted for 44% (31/70) of the cases, while viral meningitis and bacterial meningitis accounted for 14% and 10% respectively. Mixed meningitis was seen in 23% (16/70) of the cases, with 75% (12/16) of these being a coinfection by tuberculous and cryptococcal meningitis. Median CD4 count for all cases of meningitis was 64 *cells/µl*; it was 16 *cells/µl* for cryptococcal meningitis and 96 *cells/µl* for tuberculous meningitis. The most common triad of clinical presentation of meningitis were headache (77%), neck pain/neck stiffness (39%) and photophobia (35%), and only 8% of patients had fever. Median length of hospitalisation was 11 days, while mortality was 16% (20/122). Predictors for mortality from the study were: tuberculous meningitis, headache, raised adenosine deaminase in the cerebrospinal fluid, raised C-reactive protein, and a baseline renal impairment.

Conclusion: Cryptococcal and tuberculous meningitis are the most prevalent aetiologies of meningitis in HIV infection. With adequate treatment, however, mortality from meningitis is on the downward trend. Meningitis must be considered in patients with advanced HIV disease. The possibility of multiple aetiologies should also be explored in these patients.

Keywords: meningitis, cryptococcal meningitis, tuberculous meningitis, opportunistic infection, human immunodeficiency virus (HIV).

CHAPTER 1: INTRODUCTION

1. INTRODUCTION

1.1. Introduction and background

It is well-known that Human Immunodeficiency Virus (HIV) infection in its advanced stage leads to a wide spectrum of neurological complications, causing severe illnesses such as meningitis, toxoplasmosis, lymphomas, dementia, seizures, stroke, encephalopathy and psychiatric disorders (Schutte 2013; Spudich & Ances 2017; Ritarwan 2018).

Up to 40% of people living with severe immune suppression may have a neurological disorder (Schutte 2013; Spudich & Ances 2017), and these neurological disorders may be the first manifestation in people living with HIV and AIDS (Spudich & Ances 2017; Ritarwan 2018).

Over the past two decades, in South Africa, there has been dramatic change in the prevalence, morbidity and mortality of HIV, with the disease incidence peaking between 1997 and 2003 and has since declined steadily (Johnson, Dorrington & Moola, 2017).

With the introduction first of universal access to antiretroviral therapy (ART), and then universal test and treat, new diagnostic technologies, drugs regimen and guidelines for the management of HIV (Maartens & Goemaere 2014), there has been a rapid reduction in the prevalence of opportunistic infections (Maartens & Goemaere 2014; Matinella, Lanzafame & Bonometti 2015; Ritarwan 2018).

However, the mortality of neurological complications and opportunistic infections is still high in untreated people living with HIV, among individuals defaulting treatment, as well as in persons unaware of their HIV status (Matinella et al, 2015).

Meningitis remains the leading cause of death from neurological causes among people living with severe immune suppression; it accounts for up to 60% of all neurological deaths among

people living with HIV and AIDS (Schutte 2013; Croucher & Winston, 2013; Veltman, Bristow & Klausner, 2014).

Defined as a clinical syndrome characterized by inflammation of the meninges, meningitis affects the membranes that cover the brain and spinal cord (Thinyane, Motsemme & Cooper 2015). It is an extremely serious condition and a leading cause of severe illness and death in sub-Saharan Africa (Veltman *et al* 2014; Rajasingham, Smith, Park & Jarvis 2017).

The presentation and aetiology of adult meningitis have been altered substantially by the HIV epidemics, cryptococcal and tuberculous meningitis being the most prevalent types of meningitis among people living with HIV and AIDS, (Jarvis, Meintjes, Williams, Brown, & Harrison, 2010; Schutte 2013; Veltman *et al* 2014; Boaz 2016). Together, they account for about three-quarters of all cases of meningitis (Boaz 2016). Other types of meningitis such as bacterial meningitis and aseptic meningitis also continue to be important public health problems among people living with HIV (Boyles & Mendelson, 2013; Basiri & Ahmed, 2015).

Advanced HIV-infection can make interpretation of both clinical and laboratory findings difficult (Jarvis et al, 2010; Boaz, 2016); confirmation of meningitis requires lumbar puncture (LP) and examination of cerebrospinal fluid (CSF); and imaging techniques such as computed tomography (CT) scanning and magnetic resonance imaging (MRI) are also useful for making diagnosis and detecting complications (Sloan & Parris, 2014; Veltman 2014; Boaz, 2016). Despite these, the diagnosis of certain types of meningitis remains difficult (Boaz 2016).

Meningitis is associated with high mortality and poor prognosis (Veltman *et al* 2014). Risk of mortality is correlated with the clinical stage at presentation: late presentation, low level of consciousness, diagnostic difficulties, high viral load and CD4 count of less than 200 cells/μl have all been associated with high risk of mortality (Vinnard & McGregor 2009; Sloan & Parris 2014).

1.2. Problem statement

Studies done in South Africa have shown that despite improved access to ART in Africa and the declining trend, the prevalence (Johnson *et al,* 2017), morbidity and mortality from meningitis remain unacceptably high with currently available treatment regimens (Park *et al* 2009; Jarvis *et al* 2010; Matinella et al, 2015). Furthermore, there is limited availability to rapid and accurate diagnosis of meningitis in resource-limited settings: diagnosis still depends on invasive procedures such as lumbar puncture, some standard diagnostic tests have low sensitivity; and other methods like CT scan and MRI are expensive and not readily available (Sloane & Parris: 2014; Veltman 2014, Boaz 2016; Britz, Perovic & von Mollendorf, 2016).

Against this background, it is important to understand current clinical profiles, diagnostic strategies and outcomes of meningitis at Livingstone tertiary hospital, in order to assess whether these profile and outcomes compare with other settings in order to inform quality improvement strategies; whether these diagnostic strategies being adopted can be improved, and to determine whether new treatment guidelines need to be developed or adapted.

1.3. Research question

What are the aetiologies, clinical characteristics, diagnostic approaches and treatment outcomes of meningitis among adults living with HIV and AIDS admitted to the medical wards of Livingstone tertiary hospital in Port Elizabeth?

1.4. Purpose of the study

The purpose of this study is to examine the occurrence of meningitis in adults living with HIV and AIDS admitted to the medical wards of Livingstone tertiary hospital in Port Elizabeth, and determine the prevalence of its aetiological types, clinical presentations, causative agents, diagnostic approaches, as well as treatment outcomes and predictors of prognosis.

Justification: This research is important in determining the most important organisms that contribute the highest to the local burden of meningitis among individuals living with HIV infection in a large tertiary setting. It also seeks to clarify the relationship between immune suppression and these neurological opportunistic infections, to explore their clinical characteristics, diagnostic features including blood workup, the treatment outcomes such as length of hospital stay, recovery or mortality from the disease, as well as factors determining prognosis for these infections among people living with HIV and AIDS in Port Elizabeth and the surrounding areas.

1.5. Specific objectives

The specific objectives of this study are:

- To describe the clinical symptoms and signs, and diagnosis of meningitis among people living with HIV and AIDS admitted to the medical wards of Livingstone tertiary hospital;
- To determine the different laboratory-confirmed aetiological agents causing meningitis;
- To describe the treatment outcomes of meningitis (length of hospitalisation, in-hospital mortality, or recovery and discharge) in these patients;
- To determine factors associated with meningitis treatment outcomes.

CHAPTER 2: LITERATURE REVIEW

2. LITERATURE REVIEW

2.1. Introduction: the burden of meningitis among people living with HIV and AIDS

The HIV-epidemic has dramatically affected the spectrum of central nervous system (CNS) diseases in sub-Saharan Africa; and more evidently in the background of advanced HIV disease and severe immune suppression (Cohen et al, 2010, Sloan & Parris 2014; Veltman *et al*, 2014).

The World Health Organization (WHO) in their guidelines, defines advanced HIV disease as CD4 cell count less than 200 cells/μl, or the presence of severe illnesses which are caused or aggravated by HIV infection (WHO 2017; Coetzee *et al*, 2018). These opportunistic severe illnesses are described by the WHO as "stage 3 or 4" events, and by the Centres for Disease Control and Prevention (CDC) as AIDS-defining illnesses (CDC 2008; WHO, 2017). They include neurological conditions such as meningitis, HIV-related encephalopathy and CNS lymphomas and toxoplasmosis (CDC 2008; WHO, 2017). They are called "opportunistic" because they take advantage of the already weakened immune system to cause devastating illnesses (Park *et al* 2009; Veltman *et al* 2014; Ritarwan 2018).

Historically, in the African meningitis belt, bacterial pathogens such as *Neisseria meningitidis* and *Streptococcus pneumoniae* have been the most common aetiologies, resulting in an estimated 800,000 cases between 1996 and 2010 (Rajasingham *et al*, 2017). An increasing prevalence of *Mycobacterium tuberculosis* and *Cryptococcus neoformans* has however been reported to be associated with the HIV epidemic (Veltman *et al*, 2014).

Park *et al* (2009) in their work show that sub-Saharan Africa has the highest yearly burden of cryptococcal meningitis with estimated incidence of 720,000 cases per year, and 624,700 deaths within three months of being infected. Coetzee *et al* (2018) in their study however found

the global incidence of meningitis had markedly reduced to 223,100 cases per annum, with Sub-Saharan Africa reporting the highest incidence of 162,500 cases annually.

HIV infection contributes to the overall incidence, prevalence and poorer outcomes of meningitis (Bhagwan & Naidoo 2015). For example, in populations with a generalized HIV epidemic, the estimated relative risk of HIV-infected individuals developing tuberculous meningitis is 20.6 compared to those HIV negative (Bhagwan & Naidoo 2015). Patients with advanced HIV disease are more vulnerable to meningitis and more predisposed to increased morbidity and mortality, even with efficacious and prompt therapy (Spudich & Ances, 2017; Coetzee 2018). This is relevant in South Africa, where approximately 10% of persons living with HIV still present to care facilities with CD4 count of less than 100 cells/μl, despite the widespread availability of antiretroviral therapy (Coetzee 2018).

Cryptococcal and tuberculous meningitis present with a similar clinical picture of chronic meningitis and differentiation between the two conditions on clinical grounds is practically not possible (Cohen et al, 2010; Boaz 2016). Likewise, basic CSF characteristics are frequently indistinguishable as both organisms classically produce a lymphocytic pleocytosis with high CSF protein levels (Cohen et al, 2010).

The predominance of chronic opportunistic meningitis in people living with HIV is associated with a higher risk of mortality and long-term complications (Bhagwan & Naidoo 2015; Thinyane 2015). Long term sequelae of meningitis in adults include hearing and visual loss, seizures, and cognitive impairment (Thinyane 2015).

Cryptococcal and tuberculous meningitis are strongly associated with HIV infection: they are the most important causes of illness and death from neurological causes among people living with HIV and AIDS and therefore, they must always be considered when evaluating meningitis in these individuals (Park *et al* 2009; Jarvis *et al* 2010; Veltman *et al* 2014; Britz *et al* 2016).

2.2. Clinical presentation of meningitis

The symptoms of meningitis among people living with HIV and AIDS may vary depending on the cause (Boaz 2016). Being a clinical syndrome characterized by inflammation of the tissues covering the brain and spinal cord, the clinical features of meningitis are neurological in nature and are described as meningism (Sloane and Parris 2014; Thinyane *et al*, 2015).

In a South African study by Bhagwan and Naidoo (2011), meningitis was suspected in any patients who had meningeal symptoms of headache, neck stiffness, photophobia and vomiting – alone, or in combination with fever, altered level of consciousness, or focal neurological signs. They described the most common combination of clinical features of meningitis as headache and neck stiffness – seen in 78.6% of patients, fever was seen in only 1% of patients, while the triad of headache, vomiting, and neck stiffness was observed only in 35.7% (Bhagwan and Naidoo 2011). Thinyane *et al* (2015) in their study also described the features suggestive of meningitis as headache, neck stiffness, fever, photophobia, and/or altered mental status.

Boaz (2016) further described the main feature of cryptococcal meningitis as headache, stating that patients with tuberculous meningitis tend to be admitted with marked impairment of consciousness (Boaz 2016). Sloane and Parris (2014) stated that cryptococcal meningitis usually presents with subacute headache and confusion, the intracranial pressure is often elevated, leading to cranial nerve palsies and seizures; noting that altered mental state is associated with higher mortality (Sloane and Parris 2014). While cryptococcal meningitis is subacute or chronic, tuberculous meningitis may present as either acute or chronic meningitis (Vinnard 2009; Sloane and Parris 2014).

Vinnard (2009) stated that tuberculous meningitis is associated with nonspecific prodrome of fatigue, malaise, anorexia, vomiting, fever, and headache; a depressed level of consciousness,

personality changes and cranial nerve palsies, and an active pulmonary tuberculosis. The end-stage illness is characterized by deep coma, along with spasticity and abnormal posturing (Vinnard 2009).

Coetzee *et al* (2018) noted that cryptococcal meningitis is exclusive to HIV-positive patients with severe immune suppression and CD4 count of less than 100/μl, hence the Cryptococcal Antigen (CrAg) reflex testing in South Africa's National Health Laboratory Service (NHLS) for all patients with CD4 count of less than 100/μl (Coetzee *et al* 2018).

Acute presentations of tuberculous meningitis may be clinically indistinguishable from bacterial meningitis, and there are no diagnostic criteria based on clinical presentation to distinguish between cryptococcal meningitis and bacterial meningitis (Vinnard 2009, Thinyane 2015). There is also the possibility of a coinfection with more than one type of meningitis and this should be considered in all cases of meningitis (Boaz 2016; Thinyane 2015; Vinnard 2009).

2.3. Laboratory diagnosis and treatment of meningitis

There are a variety of organisms that cause this illness, such as *Streptococcus pneumoniae, Neisseria gonorrhoea, Mycobacterium tuberculosis and Cryptococcus neoformans* (Veltman 2014; Thinyane 2015; Boaz 2016). To make a diagnosis of meningitis, clinical, radiological, microbiological, and other laboratory findings must be evaluated (Veltman 2014; Thinyane 2015; Boaz 2016). While clinical features are useful in identification of suspected cases of meningitis, confirmatory diagnosis of meningitis and of the aetiological type of meningitis requires lumbar puncture and examination of CSF (Sloane & Parris 2014).

The diagnosis of meningitis depends almost entirely on the invasive procedure of LP, and CSF analysis (Sloan and Parris 2014). Thus, in conditions where LP is not appropriate, unsafe or contraindicated, or when there is a lack of LP equipment or laboratory infrastructure, there arises a diagnostic challenge (Marx et al, 2011; Sloan and Parris 2014). These may result in

underestimation of the disease burden, poor treatment and increased mortality. CSF characteristics, aetiological classification and treatment of meningitis are explained below:

2.3.1. Cryptococcal meningitis

Laboratory diagnosis is rarely a problem in HIV-positive patients with cryptococcal infection, due to the high organism load in the CSF, leading to easy detection on testing (Boaz 2016; Coetzee *et al* 2018). A diagnosis of cryptococcal meningitis is made by the presence of a positive India ink stain in the CSF; or the detection of cryptococcal antigen (CrAg) in the CSF sample – either by a latex-agglutination test or by lateral flow immunoassay (Sloane and Parris 2014; Thinyane 2015; Boaz 2016; Coetzee *et al* 2018). Radiology has limited roles in the diagnosis of cryptococcal meningitis, but neuroimaging techniques CT and MRI scans are useful for the detection of complications (Sloane and Parris 2014).

Treatment of cryptococcal meningitis consists of three phases: induction, consolidation, and maintenance (Sloane and Parris 2014; Boaz 2016). Current guidelines emphasize the importance of potent fungicidal drugs during induction therapy because the rate of clearance of the fungus from the CSF during the first 2 weeks, known as early fungicidal activity predicts 10-week survival and long term prognosis (Sloane and Parris 2014; Tenforde, Shapiro, Rouse, Jarvis, Li, Eshun-Wilson, & Ford 2018).

According to the WHO (2018) and a systematic review by Tenforde *et al* (2018), the following is recommended as the preferred induction regimen: a short-course (one-week) amphotericin B deoxycholate and flucytosine, followed by fluconazole on days 8 to 14. Alternative recommended regimens include two weeks of fluconazole (1200 mg daily) and flucytosine; two weeks of Amphotericin B and fluconazole; or one week of Amphotericin B with two weeks of fluconazole (Tenforde *et al* 2018; WHO 2018). Consolidation phase is with fluconazole 400-

800 mg daily for eight weeks, while maintenance phase is with fluconazole, 200 mg daily (WHO 2018).

2.3.2. Tuberculous meningitis

Diagnosis of tuberculous meningitis is difficult, due to factors such as the low sensitivity of standard smear for acid-fast bacilli in the CSF and the slow growth of *M. tuberculosis* in conventional CSF culture (Marais et al 2011; Marx & Chan 2011; Boaz 2016; Torok 2017).

Analysis of CSF however still plays a central role in the diagnosis of tuberculous meningitis (Vinnard 2009). The characteristic CSF findings in tuberculous meningitis include CSF pleocytosis (raised white cell count in the CSF) with lymphocytic predominance, a low glucose and elevated protein levels (Vinnard 2009; Marx & Chan 2011; Thinyane 2015). These CSF characteristics are however not specific to tuberculous meningitis and are frequently indistinguishable from cryptococcal meningitis as both organisms classically produce a lymphocytic pleocytosis with high CSF protein levels and low glucose levels (Cohen et al, 2010). Thinyane (2015) argued that, to make a diagnosis of tuberculous meningitis, these CSF findings may be used in combination with clinical symptoms, presence of active tuberculosis at another site (e.g., the lungs), with brain CT findings, or by trial of tuberculosis treatment to check for clinical improvements.

Newer diagnostic methods for tuberculous meningitis have hence been developed. These include CSF adenosine deaminase (ADA) levels, which has high sensitivity and specificity for the diagnosis of tuberculous meningitis (Marx and Chan 2010). Others include molecular diagnostic tests, such as GeneXpert MTB/RIF (Mai & Thwaites 2017; Boyle 2018). However, with the sensitivity of 70.5% and specificity of 87.5% , they cannot rule out the disease (Padayachee & Bhigjee 2007; Mai & Thwaites 2017; Boyle 2018).

The atypical CSF findings in tuberculous meningitis may include neutrophil predominance, acellular or even normal CSF (Boaz 2016). Such findings may mislead clinicians, resulting in a delayed or missed diagnosis of tuberculous meningitis. Laboratory methods to improve the rapid diagnosis of tuberculous meningitis are thus urgently required.

Neuroimaging techniques such as brain CT is helpful in confirming the diagnosis of tuberculous meningitis (Marx & Chan 2010; Thinyane 2015). CT findings that are suggestive of tuberculous meningitis include basal meningeal enhancement, cerebral infarcts, mass lesions, or hydrocephalus (Thinyane 2015, Vinnard 2009).

Current WHO guidelines for the treatment of tuberculous meningitis are based on those developed to treat pulmonary tuberculosis, and suggest treatment with two months of rifampicin, isoniazid, pyrazinamide and ethambutol, followed by up to ten months of rifampicin and isoniazid for all patients (Marx & Chan 2011; Davis, Meintjes and Wilkinson 2018). A systematic review by Jullien, Ryan, Modi and Bhatia (2016) however found no evidence of high relapse rates in people treated for six months compared to those treated for longer duration and also revealed higher mortality and poor adherence among patients treated for longer durations. Prasad, Singh and Ryan (2016) in their review also found corticosteroid therapy to be useful in reducing mortality from tuberculous meningitis, at least in the short term.

2.3.3. Bacterial meningitis

Bacterial meningitis is diagnosed based on a positive CSF Gram stain and culture, or a positive bacterial antigen test (Thinyane 2015). The culture result is highly sensitive in patients with bacterial meningitis who have not been treated with antibiotics therapy prior to LP (Boaz 2016; Veltman 2014). However, CSF cultures may take up to 48 hours for organism identification (Boaz 2016); thus other rapid diagnostic tests are often considered to determine the bacterial

aetiology of meningitis. These tests include the gram stain, latex agglutination test and polymerase chain reaction (Thinyane 2015; Boaz 2016).

In a study by Jarvis *et al* (2010), *Streptococcus pneumoniae* accounted for 90% of all cases of culture confirmed bacterial meningitis, and *Neisseria meningitides* 3%; while gram-staining was positive in 85% of the patients. The study also revealed that bacterial meningitis contributed only for 8% of all forms of meningitis (Jarvis *et al*, 2010).

Typical CSF findings for bacterial meningitis are CSF pleocytosis with polymorphonuclear cell predominance, low glucose, and elevated protein (Thinyane 2015; Boaz 2016).

The outcome of bacterial meningitis critically depends on the rapid initiation of bactericidal antibiotic therapy and adequate management of septic shock (Nau, Djukic, Spreer, Ribes, Eiffert 2015). In community-acquired meningitis, the choice of an optimum initial empirical antibiotic regimen depends on the regional resistance patterns; while dexamethasone is recommended as adjunctive therapy (Nau *et al* 2015).

2.3.4. Viral meningitis

According to Thinyane (2015), viral meningitis is diagnosed when patients have clinical features of meningitis, but negative CSF gram stain and cultures for bacteria, negative CSF cryptococcal antigen test, and nonviral causes of aseptic meningitis have been excluded. The prevalence of viral meningitis may be higher than reported because diagnostics tests for detection of viruses are limited (Veltman 2014). A study by Jarrin & Sellier (2016) revealed that 40% of patients with aseptic meningitis, on further investigation, eventually had a diagnosis of viral meningitis.

The most commonly involved viruses are Epstein-Barr Virus (EBV), Enterovirus, Herpes Simplex Virus (HSV) and Varicella Zoster Virus (VZV), and they are often detected by

polymerase chain reaction assay (Thinyane 2015; Jarrin & Sellier 2016; Rajasingham, *et al*, 2017; Tunkel 2018). Rajasingham, *et al*, (2017) in their study identified EBV in 42% of patients tested. Typical CSF findings are CSF lymphocytic predominance, normal or slightly elevated protein, and normal glucose (Thinyane 2015).

2.3.5. Lymphocytic (aseptic) meningitis

In aseptic meningitis, patients have a similar clinical presentation to other forms of meningitis and laboratory evidence for meningitis such as CSF lymphocytic pleocytosis, but no pathogen is identified in the CSF (Veltman 2014; Boaz 2016; Tunkel 2018). In normal conditions, there are less than 5 cells/μL of CSF (Veltman 2014; Boaz 2016; Tunkel 2018).

Viruses are the main causes of aseptic meningitis syndrome (Boaz 2016; Jarrin & Sellier 2016; Tunkel 2018). In contrast to other forms of meningitis, however, aseptic meningitis have a self-limited course; the disease is rarely life-threatening, and recovery is usually complete without any specific therapy or specific control measures (Boaz 2016; Tunkel 2018).

2.4. Treatment outcomes

Treatment outcomes of meningitis may be measured by length of hospitalisation, mortality from the disease, case fatality of the aetiological types, discharges, need for escalation of care or complications (Jarvis 2010; Bhagwan & Naidoo 2015; Thinyane 2015; Boaz 2016). In the study by Thinyane *et al* (2015), the median hospital stay for discharged patients was 11 days, (interquartile range IQR 6–25 days), and for those who died, 8 days, (IQR 2-73 days), with more than half (56%) of the deaths occurring during the first 7 days of hospital admission; while Boaz (2016) noted a median of two weeks hospitalisation.

Mortality from meningitis was high among different studies. Boaz (2016) found 40% mortality for all patients with laboratory confirmed meningitis, which was comparable to 43% found in the study by Thinyane (2015) and 42% by (Rajasingham, *et al*, 2017). According to Bhagwan

& Naidoo (2015), the case fatality rate for cryptococcal meningitis alone was 11.1% and 66% for tuberculous meningitis. Boaz (2016) noted 75% mortality in tuberculous meningitis, and 36% mortality for cryptococcal meningitis, and 32% for aseptic meningitis, while Bhagwan & Naidoo (2015) noted 40% mortality among patients coinfected by tuberculous and cryptococcal meningitis.

2.5. Predictors of mortality

Thinyane *et al* (2015) in their study found severe renal impairment (eGFR < 30 mL/min) as the only variable significantly associated with in-hospital mortality among their study participants, while Boaz (2016) reported the baseline CD4 and colour of the CSF as the predicting factors.

2.6. Conclusion

High rates of HIV in a population may make interpretation of CSF findings difficult (Jarvis 2010). It is therefore important to take this into consideration when investigating and managing patients with suspected meningitis. Management of these patients include several components such as: a timely identification of the aetiological organism, finding and instituting appropriate therapy and managing complications like raised intracranial pressure, stroke and seizures (Thinyane *et al* 2015; Nau *et al* 2016). Delaying or mismanaging any of those components can result in significant morbidity and mortality, and long term sequelae, including hearing loss, focal neurological deficits, learning disorders and seizures (Thinyane *et al* 2015; Nau *et al* 2016).

CHAPTER 3

3. METHODOLOGY

3.1. Research design

This is a retrospective medical records review of patients living with HIV and AIDS admitted to the medical wards of Livingstone tertiary hospital with symptoms and signs of meningitis between 1st January and 31st December 2018.

Medical record review is a type of research design in which pre-recorded, patient-centred data are used to answer one or more research questions or to evaluate relationships between one or more biomedical, treatment, and/or demographic variables, and one or more outcome measures in patients (Matt & Matthew 2013; Sakar 2014). The data used in such reviews may include a wide range of information such as results of laboratory tests, nursing and physician notes, summary reports; and may exist in many forms such as electronic databases, results from diagnostic tests, and notes from health service providers (Matt & Matthew 2013).

Justification: Medical record review is the study design of choice in this research. Meningitis is a severe CNS infection; this implies that patients admitted for meningitis have severe neurological symptoms such as severe headache, reduced levels of consciousness and they may be disorientated for a prolonged period. There is also high mortality associated with the disease with patients dying shortly after admission. These pose an ethical challenge and feasibility issue, because for many patients with meningitis, obtaining consent, interviews and self-completed questionnaires are impossible. Medical records review therefore offers a practical solution to these challenges and an opportunity to study these patients.

3.2. Study setting

The study was conducted at Livingstone – a tertiary level, referral and teaching hospital in Port Elizabeth, Eastern Cape.

The city of Port Elizabeth is located in Nelson Mandela Bay Municipality, and, together with the nearby towns of Uitenhage and Despatch and the surrounding rural area has a population of over 1.3 million (Census 2011). According to the Eastern Cape coalition of NGOs (2014), it has an unemployment rate of 36% and vast inequalities between the different groupings. The HIV and AIDS epidemic also poses a great development challenge.

With 542 hospital beds capacity, Livingstone tertiary hospital provides health care services to the city of Port Elizabeth and the entire municipality, and its departments are managed by specialists. Due to the severity of the disease, and according to available protocols, all patients with meningitis are referred and admitted to the department of Medicine for specialist care. Therefore, its medical wards are the appropriate place for this study. However, the study might not reflect the true burden in the community.

The department of Medicine is well equipped with full complement of doctors, nurses and supporting staffs such as physiotherapists and dieticians. It runs a 24-hour acute medical unit which caters for emergencies such as meningitis.

3.3. Study population

All patients living with HIV and AIDS admitted to the medical wards of Livingstone tertiary hospital for symptoms and signs of meningitis were eligible for this study.

3.4. Inclusion criteria

- All consecutive patients admitted to the medical wards of Livingstone tertiary hospital with a clinical suspicion or confirmed diagnosis of meningitis.
- Patients must be diagnosed with HIV-infection – documented HIV-positive status is required.
- Patients must have two or more classical signs of meningeal irritation which include photophobia, neck rigidity, vomiting, headaches, fever, alteration in mental state, or fits.

3.5. Exclusion criteria

- Patients with symptoms and signs of meningitis but without reports from LP or imaging techniques were excluded from this study.
- Patients with symptoms and signs of meningitis but demised before LP or imaging techniques were performed were also excluded from the study.

3.6. Sampling method

All consecutive patients admitted to the medical wards of Livingstone tertiary hospital from 1st January to 31st December 2018 who met the eligibility criteria were recruited into the study until the predetermined sample size was met.

3.7. Sample size

For this study, the sample size required was calculated according to the following formula:

$$\mathbf{n = \{(Z_{1-a/2})^2 * p\,(1-p)\}/d^2}$$

where n = Sample size; $Z_{1-a/2}$ = Statistic for the level of confidence of 95%, 1.96; p = estimated prevalence of meningitis of 8%; and d = Precision, 0.05.

Thus: n = $[\{(1.96)^2\} * \{0.08(1-0.08)\}] / (0.05)^2$

= $\{(3.842) * \{0.08*0.92\}\} / (0.0025)$

= $\{(3.842) * (0.0736)\} / (0.0025)$

Sample size n = 0.2828 / 0.0025 = 113

Sample size was computed to comprise of 113 patient clinical records. However, following a search for patients who met the eligibility criteria and in order to avoid missing observations, the study was slightly oversampled to a total of 122 patient clinical records.

3.8. Data collection procedures

Preliminary information about the patients were collected from the admission registers from all the medical wards for all patients admitted between 1st January and 31st December 2018. These were the official registers of all admissions, and they contained the names of the patients, their hospital numbers, dates of birth, dates of admission, diagnoses, date of discharges as well as dates of death as indicated.

Patients suspected to have meningitis by the admitting medical officer all undergo lumbar puncture as part of the routine clinical assessment followed in Livingstone tertiary hospital, unless they have other conditions for which a lumbar puncture contra-indicated, in which case the patients will be referred for CT scan or MRI scanning. These patients are recorded in the admission registers as having “meningitis” or “meningitis queried”.

A sample size of 122 patients’ clinical records was recruited consecutively from all patients with the above diagnoses who meet the eligibility criteria. Their clinical records were traced, and using the data extraction tool, relevant data were extracted from the clinical records. Results of laboratory investigations for these patients were also retrieved from the National

Health Laboratory Services where such information could not be extracted from their clinical records. The data extraction tool was completed by the researcher only.

Variables included in the data extraction tool included: demographic characteristics, symptoms and signs, lumbar puncture report, laboratory results, aetiological type of meningitis, and treatment outcomes.

3.9. Pilot study

The data extraction tool was pre-tested on the clinical records of fifteen patients with meningitis admitted to the medical wards of Livingstone tertiary hospital (slightly above 10% of the calculated sample size) and who met the eligibility criteria of the study. These were however not included in the study itself.

Justification: This pilot study was done to evaluate the comprehensiveness of the questions and to assess whether the tool was able to elicit the required information from the admission register and patients' clinical records. Based on the feedbacks from the pilot test, the data extraction tool was modified such that it became less ambiguous, more feasible and more adapted to satisfy the objectives of the study.

3.10. Study variables

3.10.1. *Dependent (outcome) variables:* Aetiological type of meningitis, and treatment outcome.

3.10.2. *Independent (exposure) variables:* Demographic data, clinical characteristics; baseline immune status; reports of LP and blood investigations.

3.11. Data processing and analysis

Each data extraction sheet was checked for completeness. Data were then entered, cleaned and coded using Microsoft Excel software. Double data entry was performed for all data.

Data analysis was performed using R software (Version 1.1.463, RStudio, Inc.).

Descriptive statistics were used to summarize data and were presented in form of tables and graphs, pie charts and cross tabulations. Continuous data were presented as medians and inter-quartile ranges (IQR) while categorical data were analysed as frequencies and percentages. The associations between the primary outcomes and the continuous variables were analysed using the Students' T-Test, while Chi-squared Test and Fisher's Exact Test were used as appropriate to analyse the associations between categorical variables and the primary outcomes. Associations between variables were considered to be significant if the p value was <0.05 at 95% CI.

3.12. Validity and reliability

3.12.1. Internal validity

According to Polit & Beck (2013), validity refers to the degree to which the research instrument measures what it is designed to measure.

Efforts to prevent/reduce selection bias:

Eligibility criteria were clearly defined and adequate sample size was selected for the study. These ensured that the study sample was appropriate and representative of the study population. Also, consecutive patients who meet the selection criteria were included in the study, thus ensuring that every patient had equal opportunity to participate in the study until the sample size was met.

Eliminating possible measurement bias:

This was ensured by careful study design, as well as detailed and accurate extraction information from health records of the patients using the data extraction tool. The quality of the measurement may be limited by the quality of the folders; however, given the high standard of patient care practices, the quality of the equipment used by the hospital for patient care which are properly maintained, as well as the quality of the National Health Laboratory Services, it is possible to conclude that the measurement bias will be at a minimum.

The research instrument was also pretested to check its appropriateness, and to detect if there are flaws in the construction of the questions; and it was subsequently modified accordingly. The supervisor was also consulted for guidance throughout the process. Double data entry was performed for all data.

3.12.2. Reliability of the study

Reliability refers to the consistency with which a measure can be counted on to give the same result if the aspect being measured has not changed (Polit & Beck, 2013).

Steps to be taken to ensure reliability:

Pilot testing of the instrument was performed to determine that the variables to be measured in the checklist were not confusing but concise and clear, questions were interpreted correctly. The data extraction sheet was completed by the researcher who is familiar with the subject of meningitis; and the data extracted were checked for completeness by the researcher. Double data entry was performed for all data.

3.13. Ethical considerations

Permission to conduct the study was sought from the biomedical science research ethics committee of the University of the Western Cape, ethics reference number: BM16/5/28

(appendix 2); as well as from the Eastern Cape health research committee, reference number EC_201809_017 (appendix 3). Institutional permission to conduct research and for support from relevant departments was also sought from the ethics research committee of Livingstone tertiary hospital (appendix 4).

Potential risks to the study participants:

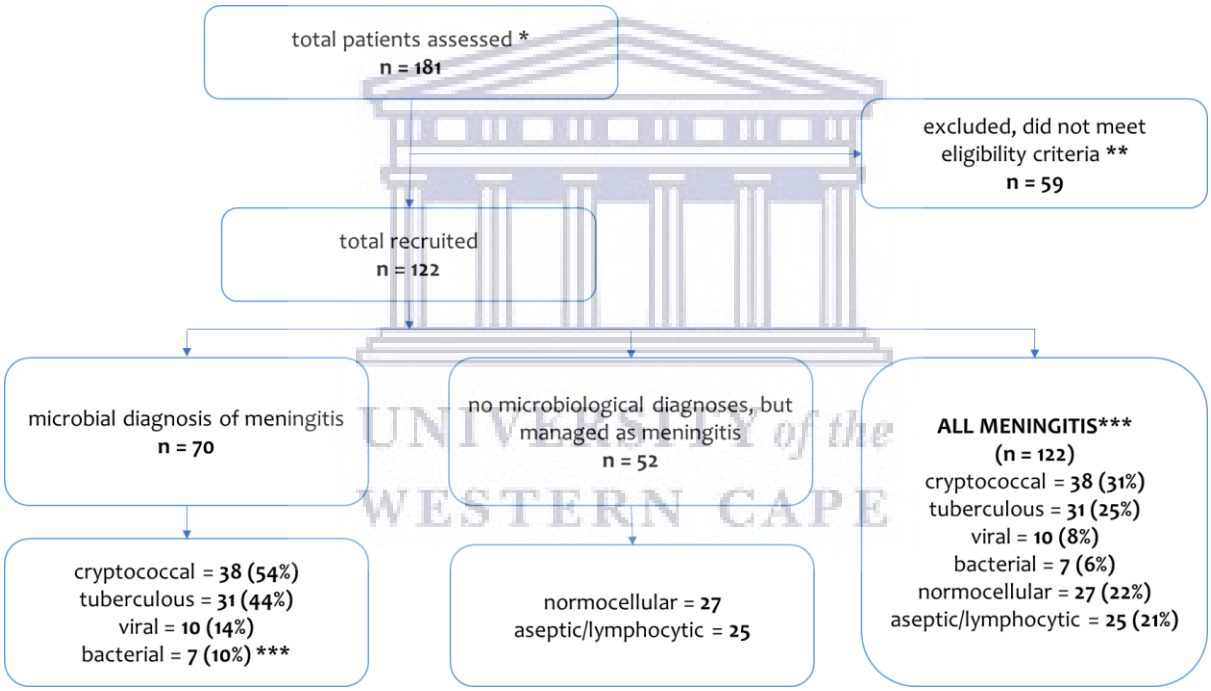
This study was not considered risky to the patients because there was no direct contact with the patients. The identities of the patients were protected throughout the course of this study.

4. RESEARCH RESULTS

4.1. Study enrolment

A total of 122 clinical records of patients who were admitted with features of meningitis between January and December 2018, and which met all the eligibility criteria were enrolled into this study.

Figure 1: Flow Chart showing the enrolment of patients' hospital records for data extraction (n = 122)



* Consecutive patient recruitment until sample size met.

** HIV negative, age <18years, no LP done or no results founds, no CNS imaging done.

*** total exceeded 100% because of the 16 patients with mixed aetiologies.

4.2. Baseline demographic and immunological characteristics

The median age of the study population was 38.5 years (IQR 31.25-47.75), with male patients constituting the majority at 57% (n = 70). The median CD4 count for all the cases of meningitis was 64 *cells/µl* (IQR 17-215), while median viral load of 24,100 *copies/mL* (IQR 1,345-276,000) (Table 1).

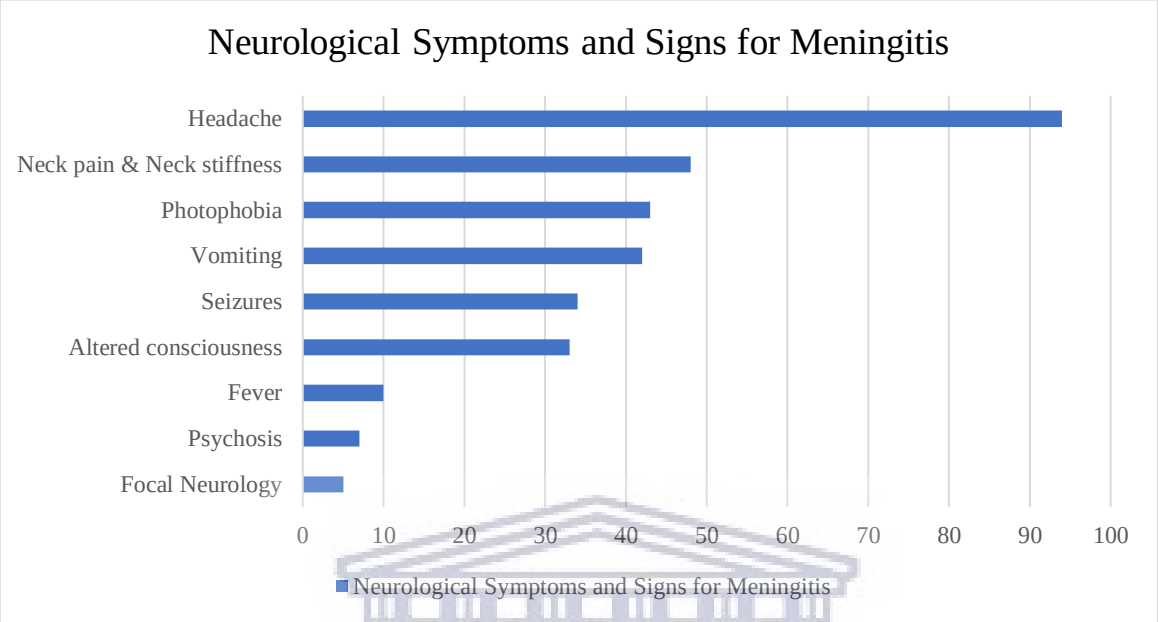
TABLE 1: Baseline demographic and immunologic characteristics and outcomes of adults living with HIV/AIDS admitted with features of meningitis (n = 122)

Characteristic	**Median (IQR) or Frequency (%)**
Age *(in years)*	38.5 (31.25-47.75)
Sex (*n & % Male)*	70 (57%)
CD4 *(cells/uL)*	64 (17-215)
Viral Load *(copies/mL)*	24100 (1345-276000)
Days of hospitalisation	11 (8-16)
Outcome: Discharged	102 (84%)
Outcome: Demised	20 (18%)

4.3. Clinical presentation

Nine neurological symptoms and signs were assessed in this study (Figure 2). Headache was the most prevalent complaint, occurring in 77% of the patients. The most common triad of clinical presentation of meningitis were headache, neck pain/neck stiffness (39% of patients) and photophobia (35%). These were followed by vomiting (34%). Seizures and alteration in levels of consciousness were also common presentations, occurring in more than a quarter of the patients. Fever, psychosis and focal neurological deficits were less common – constituting 8%, 6% and 4% respectively (Figure 2).

FIGURE 2: Neurological symptoms and signs of adults living with HIV/AIDS admitted with features of meningitis (n = 122)



4.4. Cerebrospinal findings

The cerebrospinal fluid was clear in about 80% of the patients (97/122), turbid in 15% (18/122), while it was bloody in 7 (6%) patients (Table 2).

Of the 18 patients with turbid CSF, 6 patients had bacterial meningitis, 3 patients had tuberculous meningitis, another 7 patients had coinfection by cryptococcal and tuberculous meningitis, while the remaining 2 patients had aseptic CSF.

The median CSF glucose was below average at 2.8mmol/L (1.9-3.30), while more than two-thirds of the patients (75/122) had CSF protein levels higher than the recommended 0.45g/L.

The majority of the patients (70, 57.4%) had a CSF lymphocytic predominance, and half of this number (35, 28.7%) also had raised CSF polymorphonuclear cells. All patients with raised CSF polymorphonuclear cells also had elevated CSF lymphocyte levels (Table 2).

TABLE 2: Cerebrospinal fluid analysis of adults living with HIV/AIDS admitted with features of meningitis (n = 122)

Characteristic	Value: median (IQR)	Normal
CSF Appearance		
Clear	97 (79.6%)	Clear
Turbid	18 (14.7%)	Clear
Bloody	7 (5.7%)	Clear
Biochemistry		mmol/L
Glucose	2.8 (1.9-3.3)	~ 3.0-7.0
Protein	0.74 (0.29-2.24)	0.15–0.45 g/L
Adenosine deaminase	2.3 (0.2-4.9)	<1
Cell Count		
Polymorphonuclear cells	0 (0-8.5)	0
Lymphocytes	10 (0-39)	0
Erythrocytes	2 (0-46)	0
CSF WBC Predominance		
Polymorphonuclear cells	35 (28.7%)	0
Lymphocytes	70 (57.4%)	0

Cryptococcal meningitis was confirmed in 38 (31%) patients with a positive Cryptococcal Antigen Test (CrAg/Latex Flow Assay) result (Table 3). All patients who had a positive Indian ink result also had a positive CSF CrAg test result.

Bacterial meningitis was confirmed in 7 (6%) patients – 4 patients by multiplex polymerase chain reaction, and 3 patients by bacterial antigen test. The diagnosis of bacterial meningitis

detected four cases *Neisseria meningitides*, two *Streptococcus pneumoniae*, and one case of *Escherichia coli* (Table 3). In all cases, routine culture did not yield any growth after two days.

TABLE 3: Cerebrospinal fluid aetiological diagnosis for adults living with HIV/AIDS admitted with features of meningitis (n = 122)

Characteristic	**Number of patients (%)**
Cryptococcal Antigen Test	
CrAg positive	38 (31%)
Culture / Bacteria Isolates	
Bacterial isolates positive	7 (5.7%)
Neisseria meningitides	4 (3.3%)
Streptococcus pneumoniae	2 (1.6%)
Escherichia coli	1 (0.8%)
TB Testing	
TB testing positive	31 (25%)
Viruses Detected	
Viral screen	10 (8%)
Epstein-Barr virus	7 (5.7%)
Syphilis	2 (1.6%)
JC Virus	1 (0.8%)

Viral aetiologies were identified in 10 (8%) patients. A multiplex PCR (herpes panel) was used for the detection of viruses that can cause meningitis. Antibody testing was also used. Epstein-Barr virus was detected in 7 patients, VDRL was detected in 2 patients, while JC virus was detected in 1 (Table 3). Viral screen was however not done routinely, except at the discretion

of the managing physician. Tuberculous meningitis used a combination of approaches to confirm diagnosis including positive PCR/Xpert MTB/Rif Ultra, elevated levels of adenosine deaminase and isolating *M. tuberculosis* by TB culture. A total of 31 (25%) patients were diagnosed with tuberculous meningitis through these methods, including 3 patients diagnosed with positive PCR/Xpert MTB/Rif Ultra, 1 patient by PCR/Line Probe Assay, and 3 patients by positive *M. tuberculosis* culture results (Table 3).

4.5. Prevalence of laboratory-confirmed meningitis

Of the 122 patients who presented with a clinical suspicion of meningitis, 22% (27/122) had a normal CSF and no microbiological diagnosis. A further 21% (25/122) had aseptic meningitis with CSF lymphocytic predominance, but no identifiable microbial aetiology (Table 4).

In the remainder of the patients (70/122, 57%), microbiological diagnoses were obtained. Of these, 25 patients had cryptococcus meningitis only, 16 patients had tuberculous meningitis only, while an additional 12 patients had coinfection of cryptococcal and tuberculous meningitis. Six patients developed bacterial meningitis only, while viral aetiologies were confirmed in 6 patients. Two more patients had viral and tuberculous meningitis coinfection, viral and cryptococcal coinfection occurred in 1 patient, and an additional 1 patient had coinfection of bacterial and tuberculous meningitis (Figure 3; Table 4).

For all the laboratory-confirmed cases of meningitis, the overall prevalence was 54% (38/70) for cryptococcal meningitis, 44% (31/70) for tuberculous meningitis, 14% (10/70) for viral meningitis, while bacterial meningitis had a 10% prevalence (7/70) (Table 4).

TABLE 4: Prevalence of all aetiological types of meningitis among adults living with HIV/AIDS admitted with features of meningitis

Aetiological Type	Number of patients*	Percentage ** (n=122)	Percentage*** (n=70)
CC Meningitis	38	31%	54%
TB Meningitis	31	25%	44%
Viral Meningitis	10	8%	14%
Bacterial Meningitis	7	6%	10%
Mixed Meningitis	16	13%	23%
Aseptic Meningitis	25	21%	0%
Normal CSF Finding	27	22%	0%

* Total number exceeds 122 to cater for the 16 patients who had mixed aetiologies.

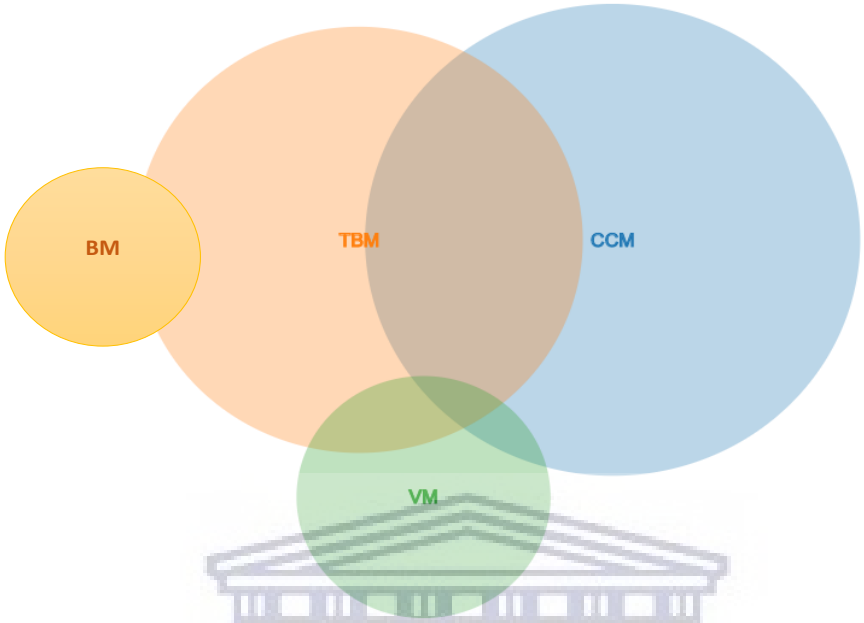
** Total exceeded 100% because of the 16 patients who had mixed aetiologies.

*** Prevalence of laboratory-confirmed aetiological types. Total exceeded 100% because of the patients who had mixed aetiologies

TABLE 5: Prevalence of mixed aetiological types of meningitis among adults living with HIV/AIDS admitted with features of meningitis (n = 16)

Mixed Meningitis	Number	Percentage
CCM – TBM	12	75%
TBM – Viral	2	12.5%
TBM – Bacterial	1	6.25%
CCM – Viral	1	6.25%

Figure 3: Prevalence of mixed aetiological types of meningitis among adults living with HIV/AIDS (n = 16)



CCM = cryptococcal meningitis (n=38). TBM = tuberculous meningitis (n=31). VM = viral meningitis (n=10). BM = bacterial meningitis (n=7). TBM^CCM=12. CCM^VM = 1.TBM^VM=2. TBM^BM=1.

4.6. A comparison of all the aetiological types of meningitis

The median ages for meningitis for all aetiological types of meningitis is comparable to the overall median of 38.5 (IQR 31.2-47.8), except for bacterial meningitis for which the median age is lower, at 20 years (IQR 16-45) (Table 6).

The median CD4 count for all aetiological types of meningitis is 64 cells/μl (IQR 17-215), while the median viral load is 24100 copies/mL (IQR 1345-276000). This median CD4 count differs widely from the median CD4 of the different aetiological types of meningitis: cryptococcal meningitis had the lowest with a median CD4 count of 18 cells/μl, tuberculous meningitis had median CD4 counts of 96 cells/μl, while the median CD4 counts for viral, bacterial and aseptic meningitis were 204 cells/μl, 178 cells/μl, and 177 cells/μl respectively.

Patients admitted with features of meningitis but who had normal CSF results were also found to have low CD4 counts of 47cells/μl (Table 6).

Table 6: Comparison of aetiological types of meningitis, based on immunologic status and demography for adults living with HIV/AIDS admitted with features of meningitis (n = 122).

	CCM ***(n = 38)***	**TBM** ***(n = 31)***	**Viral** ***(n = 10)***	**Bacterial** ***(n = 7)***	**Aseptic** ***(n = 25)***	**Normal** ***(n = 27)***
Demography						
Age *(in years)*	38 (35-43)	39 (34-47)	38 (34-39)	20 (16-45)	40 (31-49)	37 (32-51)
Male Sex	25 (66%)	16 (52%)	4 (40%)	3 (43%)	13 (52%)	16 (60%)
Immunology						
CD4 *(cells/µl)*	18 (9-52)	96 (24-162)	204 (95-274)	178 (159-196)	177 (63-463)	49 (20-202)
VL *(copies/mL)*	33,100 (872-289,500)	46,198 (1459-295,500)	4840 198-48,700)	64,010 (32,015-96005)	169,000 (4268-404,500)	14,090 (678-32,775)

Most aetiological types had predominantly clear CSF. However, it was predominantly turbid in bacterial meningitis (86%). The percentage of patients with turbid CSF in tuberculous, cryptococcal and viral meningitis were 36%, 18% and 8% respectively (Table 7).

All patients with microbiological diagnoses of meningitis had low CSF glucose levels and raised protein levels. CSF glucose level was lowest in tuberculous meningitis (1.9mmol/L; IQR 0.7-2.6), followed by cryptococcal meningitis (2.2mmol/L IQR 0.9-2.7), then viral and bacterial meningitis at 2.5mmol/L (1.3-3.5) and 2.6mmol/L (0.3-3) respectively (Table 7).

Table 7: Comparison of aetiological types of meningitis, based on CSF finding for adults living with HIV/AIDS admitted with features of meningitis (n = 122).

	CCM ***(n = 38)***	**TBM** ***(n = 31)***	**Viral** ***(n = 10)***	**Bacterial** ***(n = 7)***	**Aseptic** ***(n = 25)***	**Normal csf** ***(n = 27)***	**Normal Range**
CSF Appearance							
Clear	28 (74%)	19(61%)	8 (80%)	1 (14%)	20 (80%)	27 (100%)	clear
Turbid	7 (18%)	11 (36%)	0	6 (86%)	2 (8%)	0	clear
Bloody	3 (8%)	1 (3%)	2 (20%)	0	3 (12%)	0	clear
Biochemistry							
Glucose	2.2 (0.9-2.7)	1.9 (0.7-2.6)	2.5 (1.3-3.5)	2.6 (0.3-3)	3.2 (2.7-3.7)	3 (2.9-3.6)	3-7
Protein	1.05 (0.5-2.2)	2.06 (1.3-3.1)	1.59 (0.7-2.9)	3.41 (2.9-4.2)	0.4 (0.3-0.7)	0.27 (0.2-0.4)	0.15-0.45
ADA	3.9 (1.7-5.5)	8.1 (5.9-11.7	3.4 (2.6-3.8)	3.5 (1.2-4.6)	1.1 (0-2)	0	<1
Cell Count							
PMN cells	0 (0-11)	3 (0-37)	0	8,651	4 (0-8)	0	0
Lymphocytes	16 (2-79)	25 (12-117)	28 (22-69)	53 (5-483)	11 (6-29)	0	0
Erythrocytes	5 (0-44)	9 (0-30)	49 (0-107)	19 (0-62)	4 (0-96)	0	0
Raised WBC%							
PMN cells	32%	39%	0	100%	36%	0%	0
Lymphocytes	66%	81%	90%	70%	76%	0%	0
Coinfection	13 (34%)	15 (48%)	1 (10%)	1 (14%)	0	0	0

CSF protein was highest in bacterial meningitis (3.41g/dL), followed by tuberculous, viral and cryptococcal meningitis at 2.06g/dL (1.35-3.1), 1.59g/dL (0.68-2.9) and 1.05g/dL (0.47-2.2) respectively (Table 7). Tuberculous meningitis had a median adenosine deaminase level of 8.1 (5.9-11.7) (Table 7).

All aetiologic types of meningitis had predominance of lymphocytes in up to 90% of patients (Table 7). Less predominant were polymorphonuclear cells in about 40% patient, except in bacterial meningitis where all patients had polymorphonuclear cell predominance (Table 7). Patients with normal CSF finding blood cells in their CSF (Table 7).

TABLE 8: Outcomes of meningitis among adults living with HIV/AIDS admitted with features of meningitis (n = 122).

Aetiological Type	**Duration of hospitalisation**	**In-hospital Mortality***	**Case Fatality**
All Meningitis (n=122)	11 (8-16)	20	16%
Normal CSF Finding (n = 27)	9 (7-11.5)	4 (20%)	15%
Aseptic Meningitis (n = 25)	11 (8-17)	4 (20%)	16%
Cryptococcal Meningitis (n = 38)	15 (12.50-18.75)	5 (25%)	13%
Tuberculous Meningitis (n = 31)	11 (7-17)	9 (45)	29%
Viral Meningitis (n = 10)	11 (8.5-14.5)	1 (5%)	10%
Bacterial Meningitis (n = 7)	12 (10-12.5)	0	0%
Mixed Meningitis (n = 16)	14.5 (10.75-18.25)	3	
CCM-TBM (n = 12)	14.5 (10-18.25)	3 (15%)	25%

**Total exceeded 100% because of the 3 patients who had mixed aetiologies.

4.7. Primary outcomes of meningitis

The primary outcomes of the study are: the duration of hospital stay and in-hospital mortality.

4.7.1. Duration of hospitalisation

The median number of days of hospitalisation for all types of meningitis is 11 days (IQR 8-15 days). This was shorter among patients who had normal CSF findings, with median of 9 days (7-11.5), while longest hospital stay was among patients admitted for cryptococcal meningitis with median of 15 days (12.50-18.75). Patients with bacterial meningitis and mixed meningitis also stayed longer than the median number of days at 12 and 14.5 days respectively (Table 8).

4.7.2. In-hospital mortality

There was 16% mortality for all patients admitted with clinical features of meningitis (20/122).

Of these, tuberculous meningitis had the highest inpatient mortality with 9 deaths (45%), followed by cryptococcal meningitis with 5 deaths (25%). It should be noted that 3 patients had coinfection by cryptococcal and tuberculous meningitis, thus reducing mortality from cryptococcal meningitis alone to 2. Furthermore, 4 patients with normal CSF findings died, 1 patient died from viral meningitis (5%), and 4 from aseptic meningitis (20%). There was no mortality among patients admitted for bacterial meningitis (Figure 8).

4.8. Associations of the outcomes of meningitis

The primary outcomes of the study were the duration of hospital stay and in-hospital mortality.

By aetiological types, cryptococcal meningitis was found to be significantly associated with the number of days of hospitalisation (p-value = 0.004), while tuberculous remains the predictor for mortality by aetiology, p-value 0.043. OR = 3.12, (1.00 – 9.58) (Table 9).

By demography, age and gender were found to be not significantly associated with either mortality or length of hospitalisation (Table 10).

The baseline CD4 count and viral load were not predictors of mortality, they were however statistically significant in determining duration of hospitalisation, with *p-values* of 0.007 and <0.001 and respectively (Table 10).

Among the neurological symptoms and signs, only headache was found to be statistically associated with the primary outcomes being measured, p-value = 0.016 for mortality, and 0.036 for length of stay (Table 13).

In the CSF findings (Table 11), the only determinant for mortality was raised ADA levels (p-value = 0.016). However, they were many predictors for length of hospitalisation, including lymphocyte count (p-value = 0.5), positive CLAT (p-value = 0.002), erythrocyte count (p-value = 0.014), polymorphonuclear cell count (p-value = 0.03) and ADA (p-value = 0.029).

Potassium levels also affect the length of hospitalisation (p-value = 0.002) (Table 15). Liver function test was not significantly associated with any of the outcomes.

The renal status of the patient (urea, creatinine and glomerular filtration rate) were found to be predictors of mortality, and were all statistically associated with the duration of hospitalisation (Table 12).

For septic markers, C-reactive protein was found to be a predictor of both mortality and length of hospital stay (p-value <0.001), while WCC is a predictor of length of stay (p-value 0.003) (Table 14).

TABLE 9: Associations with outcomes of meningitis by aetiology among adults living with HIV/AIDS (n = 122).

Aetiological Type	P value for days of hospitalisation	P value for mortality	Odds Ratio for mortality
Cryptococcal Meningitis	0.004	0.603	1.50 (0.47- 5.71)
Tuberculous Meningitis	0.553	0.042	3.12 (1.00 – 9.58)
Viral Meningitis	0.974	0.690	0.49 (0.01-3.80)
Bacterial Meningitis	0.890	0.351	NA
Aseptic Meningitis	0.938	1	0.92 (0.25 – 4.19)
Normal CSF Finding	0.742	1	1.18 (0.33 – 5.32)
Mixed CCM/TBM	0.558	0.529	NA

TABLE 10: Associations with meningitis by demographic and immunological status among adults living with HIV/AIDS admitted with features of meningitis *(n = 122).*

Variable	Days of hospitalisation P value	Mortality P value
Age	0.999	0.970
Gender	0.747	0.396
CD4	< 0.001	0.188
VL	0.007	0.185

TABLE 11: Associations with outcomes of meningitis by CSF findings among adults living with HIV/AIDS admitted with features of meningitis *(n = 122).*

Variable	Days of Hospitalisation P value	Mortality P value
Glucose	0.876	0.214
Protein	0.196	0.122
ADA	0.029	0.016
Colour	0.360	0.988
Polymorphonuclear	0.03	0.249
Lymphocytes	0.0005	0.064
Erythrocyte	0.014	0.060
CLAT	0.002	0.605
Culture	0.999	0.692

TABLE 12: Associations with outcomes of meningitis by electrolyte and renal function among adults living with HIV/AIDS admitted with features of meningitis (n = 122).

Variable	Days of Hospitalisation P value	Mortality P value
Urea	< 0.001	0.034
Creatinine	0.048	0.005
GFR	< 0.001	0.534
Sodium	0.645	0.156
Potassium	0.002	0.148

TABLE 13: Associations with meningitis by neurological symptoms and signs among adults living with HIV/AIDS admitted with features of meningitis *(n = 70).*

Variable	Days of Hospitalisation P value	Mortality P value
Headache	0.016	0.036
Fever	1	0.564
Altered consciousness	0.482	0.172
Neck pain & Neck stiffness	0.179	0.102
Vomiting	0.729	0.279
Photophobia	0.17	0.626
Seizures	0.167	0.130
Psychosis	1	1
Focal Neurology	0.577	0.585

TABLE 14: Associations with outcomes of meningitis by blood count and septic markers among adults living with HIV/AIDS admitted with features of meningitis (n = 122).

Variable	Days of Hospitalisation	Mortality
Haemoglobin	0.070	0.091
WCC	0.003	0.308
Platelet	0.054	0.185
CRP	< 0.001	< 0.001

TABLE 15: A summary of the associations of outcomes of meningitis among adults living with HIV/AIDS admitted with features of meningitis *(n = 122)*

	Variables	**Length of Stay**	**Mortality**
Aetiology	CCM	0.004	
	TBM		0.042
Immune Status	CD4	<0.001	
	VL	0.007	
Symptoms	Headache	0.016	0.036
CSF	ADA	0.029	0.016
	Polymorphonuclear	0.03	
	Lymphocytes	0.0005	
	Erythrocyte	0.014	
	CLAT	0.002	
Blood	Potassium	0.002	
	Urea	<0.001	0.034
	Creatinine	0.048	0.005
	WCC	0.003	
	CRP	<0.001	<0.001

CHAPTER 5 – DISCUSSION

5. DISCUSSION

This study set out to investigate meningitis in the context of HIV infection among adults in a hospital setting to determine its aetiological types, clinical presentation, diagnostic approaches, treatment outcomes, as well as predictors of prognosis.

The median age of 38.5 years for the study sample is comparable with many previous studies (Jarvis *et al,* 2010, Cohen *et al,* 2010, Marais 2011, Thinyane 2015, Boaz 2016, Rajasingham *et al,* 2017) all of which found that meningitis is most prevalent in the third decade of life. However, there was not a consensus in the male to female ratio. While males dominated the sample in this study, Jarvis *et al* (2010) who studied 1737 cases of meningitis found an approximately 1:1 ratio, which also seen in other studies (Cohen *et al,* 2010, Rajasingham *et al,* 2017, Marais *et al,* 2011), with slight male predominance. Boaz (2016) and Thinyane (2015) however had female predominance of 68% and 57% respectively in their studies.

Meningitis in this study was found to occur in the background of advanced HIV disease, with 92% patients (112/122) having median CD4 count of less than 200 cells/*µl*, and 70% (86/122) having median CD4 count of less than 100 cells/*µl*. This is comparable to most studies reviewed for this research. While the baseline median CD4 count for cryptococcal and tuberculous meningitis in this study were 18 cells/*µl* and 96 cells/*µl* respectively, Jarvis *et al* (2010) found these to be 39 cells/*µl* and 126 cells/*µl* respectively; in Cohen *et al* (2010), they were 56 cells/*µl* and 60 cells/*µl* respectively, while in Thinyane (2015), their baseline CD4 count were 18 cells/*µl* and 119 cells/*µl* respectively. All patients with meningitis were found to have viral loads which were unsuppressed. None of the studies reviewed in this research investigated viral load as part of their variables in relation to meningitis, hence no comparison could be made.

Cryptococcal meningitis has been identified as the most common form of meningitis among individuals living with HIV, and tuberculous meningitis being the second most prevalent in sub-Saharan Africa (Cohen *et al* 2010; Jarvis *et al,* 2010; Veltman *et al,* 2014; Thinyane 2015; Rajasingham *et al* 2017). This is also demonstrated in this study at 54% and 44% respectively. Epstein-Barr virus accounted for 70% (7/10) of all viral meningitis, which is also in keeping with findings from other studies such as Rajasingham *et al,* (2017). It is interesting to note that most cases of bacterial meningitis in this study were caused by *Neisseria meningitides* (57%, 4/7), while *Streptococcus pneumoniae* accounted for 29% (2/7) of bacterial meningitis. This is in contrast to what is known in literature, where *Streptococcus pneumoniae* is the leading cause (Jarvis *et al,* 2010). It is also noteworthy, that in all cases of bacterial meningitis in this study, routine CSF culture did not yield any growth after two days, and the diagnoses were made using multiplex polymerase chain reaction and bacterial antigen test as alternative methods. This calls for the need to reassess the importance of routine CSF culture in the diagnosis of meningitis. There was a diagnostic challenge noted with tuberculous meningitis, and diagnosis was made through a composite of methods including elevated levels of CSF ADA as well as positive CSF GeneXpert MTB/RIF Ultra testing. Isolating *M. tuberculosis* by TB culture was not helpful in the acute setting – an indication for urgent improvement in the diagnostic tools for tuberculous meningitis.

This study observed a 57% (70/122) microbial diagnosis of meningitis. This is an improvement compared to other studies that have been done, which may suggest an improvement in the diagnostic approach to meningitis in the Port Elizabeth. In Cohen *et al* (2010), microbial diagnosis of meningitis was only made in 46% (263⁄573) of the cases, and this value dropped to 35% (1737/4961) in the study by Jarvis *et al* (2010). Rajasingham *et al* (2017) however, diagnosed more laboratory-confirmed aetiologies of meningitis in their study following

rigorous investigations; despite this, 29% (166/573) of patients who had CSF abnormalities in keeping with meningitis still did not have a microbial diagnosis of meningitis.

Clinically, headache is the most predominant neurological manifestation of meningitis, which is in keeping with the findings from literature; with the predominant triad of clinical features for meningitis in the Port Elizabeth setting being headache, neck pain/stiffness and photophobia. This is however not comparable to other studies reviewed: Boaz (2016) and Rajasingham *et al* (2017) found a triad of headache, fever and neck pain; Cohen *et al* (2010) found a triad of headache, fever and vomiting; while in Thinyane (2015) the most predominant features were altered mental status, neck stiffness and headache, fever and seizures, which may suggest late presentation by the patients to the hospital. Fever is not a prominent feature of meningitis in this study accounting for only 8%. This may be attributable to severe immunosuppression, whereby patients are unable to mount adequate febrile response to the illness. In this study, headache was found to contribute significantly to both prolonged hospitalisation and in-hospital mortality. Seizures, altered levels of consciousness, psychosis and focal neurology are less common clinical features in this setting.

In this study, in the CSF, all aetiologic types of meningitis had predominance of lymphocytes in up to 90% of patients, as well as low CSF glucose levels. It is also noteworthy that 10% of patients had a coinfection between tuberculous and cryptococcal meningitis; this however did not lead to an increase in mortality.

The 16% mortality and case fatalities of 13% and 29% for cryptococcal and tuberculous meningitis in this study is noted as an improvement, compared to other studies where mortality for meningitis among HIV-infected individuals was assessed. Boaz (2016) in their study found overall mortality of 36% (20/55) for meningitis, with 36% case fatality for cryptococcal meningitis and 75% for tuberculous meningitis. Thinyane (2015) in their study found 44% case

fatality for cryptococcal meningitis, and 23% case fatality for tuberculous meningitis – which they attributed to poor diagnostic tools; while Marais (2011) found 38% (45/120) inpatient mortality for tuberculous meningitis. Tenforde *et al* (2109) in their study found an overall mortality of 47% (112 of 238) and 46% case mortality for tuberculous meningitis. It is also noteworthy that this study recorded 0% mortality for bacterial meningitis and 10% case fatality for viral meningitis, compared to 40% and 90% respectively in the study by Thinyane (2015).

While tuberculous meningitis was found to be the leading cause of mortality by aetiology, cryptococcal meningitis recorded the longest median number of hospital stay of 15 days. The prolonged hospitalisation may be partly due to the treatment regimen, this however does not increase the mortality rate. Likewise, CSF abnormalities contributed significantly to prolonged hospital stay, even though they might not have any impact on mortality. Blood results that may prolong hospital stay include raised septic markers (WCC and CRP), low potassium, and deranged urea and creatinine. These may in part be due to the need to correct these blood derangements, or the need to treat other concurrent illnesses. Renal impairment significantly contributed to both prolonged hospitalization as well as in-hospital mortality; Thinyane (2015) suggested that this effect may in part be due to HIV treatment, such as tenofovir induced renal failure. And while CRP and WCC both affected duration of hospitalization, CRP is a better prognostic factor as it contributed significantly to mortality.

6. CONCLUSION AND RECOMMENDATIONS

6.1. Conclusion

This study investigated meningitis in adults living with HIV and AIDS admitted to the medical wards of Livingstone tertiary hospital in Port Elizabeth in 2018 and determined the prevalence of its aetiological types, clinical presentations, diagnostic challenges, treatment outcomes and predictors of prognosis.

A total of 122 patients who presented with clinical suspicion of meningitis and who met the eligibility criteria were enrolled for this study. The diagnosis of meningitis in the hospital depends mainly on the invasive lumbar puncture. However, only about two-thirds of patients have microbiological diagnosis. The remainder do not have a confirmed diagnosis, though they are still managed as meningitis.

This is a diagnostic nightmare.

The implication of this is the need for improved strategies for the diagnosis of meningitis in the hospital. It will be worthwhile to include as part of routine testing viral panel, bacterial antigen testing as well as GeneXpert MTB/RIF to improve diagnosis. Another advantage is the availability of radiological modalities such as CT scan and MRI within the hospital. These should be made use of more routinely.

The lower mortality rate compared to many other comparable settings is commendable. However, an mortality of 16%, out of which there is about 30% case mortality for tuberculous meningitis is unacceptably high, and improvement or adaptations in treatment guidelines may be recommended to keep mortality rate lower. While this study did not explore the short and

long term complications of meningitis, these should however be monitored, because meningitis is often associated with high morbidly as well.

This study identified a number of organisms such as *Cryptococcal neoformans, Neisseria meningitides, Streptococcus pneumoniae, Escherichia coli, Mycobacterium tuberculosis,* Epstein-Barr virus, Syphilis and JC Virus as the leading causes of meningitis within the hospital. The most common triad of clinical presentation of meningitis were headache, neck pain/neck stiffness, and photophobia; seizure and altered consciousness are fairly common, while only 8% patients could mount the febrile response to the illness. Meningitis should be suspected in every person living with HIV and AIDS who presents with these neurological symptoms.

Furthermore, since only about 20% of the patients had CD4 greater than 200 *cells/µl*. features of meningitis should be actively sought in all patients with advanced HIV disease.

The primary outcomes of the study are: the duration of hospital stay and in-hospital mortality.

A summary of associations of the primary outcomes of this study – mortality and duration of hospitalisation – can be seen in Table 15 above.

This study identified the need for improved diagnostic tools to investigate the aetiologies of meningitis. It also highlighted the need for effective management of people living with HIV and to ensure an improved immune status as a prevention strategy for severe opportunistic infections such as meningitis.

6.2. Study limitations

This is a clinical records review, and the quality of the research depends largely on the quality of the clinical records. While the hospital is reputable for the high standard of clinical notes, calibration of equipment as well as efficiency from the national health laboratory services, the retrospective nature of the study remains a limitation for the study.

This was a hospital based study and a single-centre study, which was based on the assumption that owing to the severity of the condition, patients with meningitis were all referred to the hospital for specialist care. It however did not put into account patients who demised before they could get professional care, and patients who were treated in other centres such as the private hospitals..

Diagnosis may have been limited by the availability of the laboratory tests. Certain CSF diagnostic tests such as multiplex PCR/herpes panel used for the detection of viruses, as well as PCR/Xpert MTB/Rif Ultra and culture for tuberculosis diagnosis were not done routinely for all patients. These may have impact on the findings of the study.

There is also the possibility of confounding factors causing a bias in the estimate of the impact of the exposure variables being studied. For instance, the twenty-seven patient with normal CSF findings but were included in the overall analyses. These might not have been cases of meningitis, even though they were managed as such. Multivariate analysis would have been able to control for this and other potential confounders. However this study analysis was limited to bivariate association.

Furthermore, this study did not follow up the patients who were discharged to determine the outcome following discharge to determine whether there was an improvement in their immune system, a relapse, reinfection or death.

6.3. Recommendation

A multicentre or population-based prospective cohort study of individuals with clinical suspicion of meningitis is recommended. This will help to determine aetiologic distribution, patterns, and prognosis of meningitis among adults living with HIV and AIDS.

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APPENDIX 1: DATA EXTRACTION TOOL

ANNEXURE 1: Instrument – The Data Extraction Tool

Instruction: Tick the appropriate answer.

1. SECTION A: DEMOGRAPHIC CHARACTERISTICS

1.1. Serial Number:		
1.2. Age (years):		
1.3. Gender:	a) Male	b) Female

2. SECTION B: NEUROLOGICAL SYMPTOMS AND SIGNS ON ADMISSION

SYMPTOMS AND SIGNS	YES	NO
2.1. Headache		
2.2. Fever		
2.3. Altered consciousness		
2.4. Neck pain & Neck stiffness		
2.5. Vomiting		
2.6. Photophobia		
2.7. Seizures		
2.8. Psychosis		
2.9. Focal Neurology		

3. SECTION C: BASELINE IMMUNE STATUS

3.1. CD4 count	
3.2. Viral Load	

4. SECTION E: LUMBAR PUNCTURE REPORT

4.1. CSF Chemistry			
4.1.1. CSF Glucose			
4.1.2. CSF Protein			
4.1.3. CSF ADA			
4.2. CSF colour and appearance:	a) Clear	b) Turbid	c)Bloody
4.3. CSF Cell Count			
4.3.1. Polymorphs			
4.3.2. Lymphocytes			
4.3.3. Erythrocytes			
4.4. Indian Ink – Encapsulated Yeast			
4.5. Gram Stain			
4.5.1. Neutrophil			
4.5.2. Lymphocyte			
4.6. Cryptococcal Antigen Test /LFA/Mycology			
4.7. CSF Culture Isolates			
4.8. TB: GXP/AUR/TB Culture			
4.9. Herpes (or Viral) Screen			

5. BLOOD RESULTS ON ADMISSION

5.1. Sodium	
5.2. Potassium	
5.3. Urea	
5.4. Creatinine	
5.5. Glomerular Filtration Rate	
5.6. Albumin	
5.7. ALT	
5.8. AST	
5.9. ALP	
5.10. GGT	
5.11. C-Reactive Protein	
5.12. White cell count	
5.13. Haemoglobin	
5.14. Platelets	

6. SECTION F: AETIOLOGICAL TYPE OF MENINGITIS

6.1. Normal CSF finding	
6.2. Cryptococcal Meningitis	
6.3. Tuberculous Meningitis	
6.4. Bacterial Meningitis	
6.5. Viral Meningitis	
6.6. Lymphocytic (Aseptic) Meningitis	

7. SECTION G: TREATMENT OUTCOME

7.1. Duration of hospital stay in days	
7.2. Outcome	
7.2.1. Discharge	
7.2.2. Demise	

APPENDIX 2: ETHICS APPROVAL BIOMEDICAL SCIENCE RESEARCH ETHICS COMMITTEE (BMREC) UWC

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06 June 2018

Dr K Dele-Ijabulu
School of Public Health
Faculty of Community and Health Science

Ethics Reference Number: BM16/5/28

Project Title: The aetiologies, clinical presentation, diagnostic difficulties and outcomes of meningitis among HIV-positive adults admitted to Livingstone Hospital, Port Elizabeth.

Approval Period: 23 May 2018 – 23 May 2019

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above mentioned research project.

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

Please remember to submit a progress report in good time for annual renewal.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

PROVISIONAL REC NUMBER -130416-050

FROM HOPE TO ACTION THROUGH KNOWLEDGE

APPENDIX 3: ETHICS APPROVAL, EASTERN CAPE HEALTH RESEARCH COMMITTEE

Province of the
EASTERN CAPE
HEALTH

Enquiries: Zonwabele Marile Tel no: 083 378 1202

Email: zonwabele.marile@echealth.gov.za Fax no: 043 642 3409

Date: 09 October 2018

RE: THE AETIOLOGIES, CLINICAL PRESENTATION, DIAGNOSTIC DIFFICULTIES AND OUTCOMES OF MENINGITIS AMONG HIV-POSITIVE ADULTS ADMITTED TO LIVINGSTONE HOSPITAL, PORT ELIZABETH (EC_201809_017)

Dear Dr Kemi Dorcas Dele-Ijagbulu

The department would like to inform you that your application for the abovementioned research topic has been approved based on the following conditions:

1. During your study, you will follow the submitted amended protocol with ethical approval and can only deviate from it after having a written approval from the Department of Health in writing.

2. You are advised to ensure, observe and respect the rights and culture of your research participants and maintain confidentiality of their identities and shall remove or not collect any information which can be used to link the participants.

3. The Department of Health expects you to provide a progress update on your study every 3 months (from date you received this letter) in writing.

4. At the end of your study, you will be expected to send a full written report with your findings and implementable recommendations to the Eastern Cape Health Research Committee secretariat. You may also be invited to the department to come and present your research findings with your implementable recommendations.

5. Your results on the Eastern Cape will not be presented anywhere unless you have shared them with the Department of Health as indicated above.

Your compliance in this regard will be highly appreciated.

SECRETARIAT: EASTERN CAPE HEALTH RESEARCH COMMITTEE

APPENDIX 4: ETHICS APPROVAL, LIVINGSTONE TERTIARY HOSPITAL

Province of the
EASTERN CAPE
HEALTH

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31 October 2018

DR KD Dele-Ijagbulu
Dora Nginza Hospital

Via email: kemiowonibi@gmail.com

Dear Dr Dele-Ijagbulu,

Re: REQUEST TO BE GRANTED PERMISSION TO DO RESEARCH – *"Presentation and Outcomes of Meningitis in People living with HIV and AIDS in Port Elizabeth, South Africa."*

Your request to do research at Livingstone Hospital received on 30 October 2018, refers.

Authorisation is herewith granted to do your research at Livingstone Tertiary Hospital (this includes the PE Provincial Hospital site).

Kindly contact Dr Nomvete the HOD of Internal Medicine on Tel 041 405 2373. Dr Nomvete will assign a staff member to assist you with the necessary logistical arrangements.

You are to ensure that your study does not disrupt services and you must maintain strict confidentiality at all times.

On conclusion of your study, a research report detailing your findings and recommendations is to be made available to the hospital.

May I take this opportunity to wish you success with your studies.

DR MJ MASELOA
SENIOR MANAGER MEDICAL SERVICES
MJM/jm

Together, moving the health system forward

Fraud prevention line: 0800 701 701
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