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## Clinical and Therapeutic Aspects of Cryptococcal Meningitis in West Africa

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### 1. Introduction

*Cryptococcus meningitis* is the most severe form of cryptococcal infections that infects the brain parenchyma and sub-arachnoid space. It often progresses to fatal disease states when it goes untreated. The clinical presentation and disease course of cryptococcal infection is partially marked by changes that occur as a result of certain medical conditions including, use of glucocorticoids or other immunosuppressive drugs, diabetes, as well as the immune status of the host (Chuck, 1989; Dismukes, 1988). Mostly, the disease affects people with a compromised immune system and is found in people with advanced HIV infection and AIDS, with the major burden in South-East Asia and Africa (Mwaba, 2001; Maher, 1994; Moosa, 1997).

The infection itself is caused by inhalation of a yeast-like round fungus with a polysaccharide capsule, known as *Cryptococcal neoformans*, and disseminates from the lungs. This fungus is the only pathogenic species of the genus *Cryptococcus*. Based on the capsule components four serotypes of *C. neoformans* (A, B, C and D) have been isolated, and the species is divided into two forms. Each serotype has different epidemiologic and pathogenic profile and their presence suggests an environmentally unfriendly atmosphere for people with a defective T cell function. Consequently, the common forms of *C. neoformans* that affect humans in Europe and parts of US is *C. neoformans* var *neoformans*, whereas in tropical areas such as the Far East, Africa and Australia, *C. neoformans* var *gattii* is the common form of cryptococcal infection (Gari-Toussaint, 1996). *C. neoformans* var *gattii* is also thought to be ecologically resident on Eucalyptus trees (Ellis, 1990). An outbreak of Cryptococcosis in healthy humans and animals in Vancouver Island, Canada, and the subsequent isolation of *C. neoformans* var *gattii* in Washington and Oregon in the US, have now led to the understanding that this species is not restricted to tropical and sub-tropical climates alone (Datta, 2009). Rather it has a wider geographic distribution and can also thrive in temperate climates, as well as on species of trees other than Eucalyptus (Datta, 2009).

Estimates indicate that worldwide, the burden of human cryptococcal infections ranges between 2 to 30 % and most infected patients have HIV/AIDS (Bicanic, 2006; French, 2002). An observation in the US in 1990 showed an increase to 5000 cases of *cryptococcal meningitis* infection in AIDS patients, compared to 300 cases in 1980 where half of these cases were

apparently without signs of immune suppression. In most nations, the effective adoption of antiretroviral therapy (ART) has led to a dramatic decrease in *C. neoformans* infection (Mirza, 2003). In the US for instance, only 7 % of 2087 AIDS patients were found to have cryptococcoses whereas, in France the incidence dropped to 100 cases per year due to the introduction of triple antiretroviral therapy (Steven, 1989). In most parts of Africa however, the HIV epidemic led to the emergence and resurgence of many opportunistic infections including *cryptococcal meningitis*, mycobacteria, and cytomegalovirus. Lack of full access to ART in West Africa, resulted in *cryptococcal meningitis* becoming the second opportunistic infection to cause fatal disease, after mycobacteria in late stage HIV-infected patients (Okongo, 1998; Mwaba, 2001). For instance, between 1993 and 2006, *C. neoformans* accounted for 0.7 % of meningitis cases in Dakar, Senegal and 2.5 % at Point G Teaching Hospital in Mali (Soumare, 2005c; Coulibaly, 2005). By comparison, in 2006, 33 cases out of 3655 (0.9 %) hospitalized patients were found to be infected with *cryptococcal meningitis* in Cameroon (Mbuagbaw, 2006).

In West Africa, diagnosis and treatment of *cryptococcal meningitis* is particularly faced with many difficulties including problems associated with efficiency of the healthcare system in these countries, poverty rate and educational status of those infected. In the text that follows we summarize our understanding of the current challenges faced in the clinical diagnosis and treatment of this disease in this region, and make suggestions for future consideration.

## 2. Epidemiology

Although considerable efforts have been made to estimate the number of cases of *cryptococcal meningitis* and the percentage of those infected by *Cryptococcal neoformans*, there is still gaps in the knowledge of true estimates worldwide (Harrison, 2009). Current reports show that globally there are approximately 957, 900 cases of *cryptococcal meningitis* occurring every year, with majority of these infections found in areas of high HIV prevalence (Park, 2009). Of this figure, lack of adequate resources and funding, lack of early diagnosis, access to treatment and an ineffective distribution of ART results in the deaths of between 125,000 and 1,124,900 cases shortly (3 months) after the infection (Park, 2009). In Uganda *cryptococcal meningitis* disease was found to cause 17 % of deaths among HIV-1-infected adults. In South Africa, between 13-44% of all deaths among 3 HIV-seropositive cohorts were reported to be associated with *Cryptococcus neoformans* infection (Bicanic, 2006). Globally, the incidence rates among people with HIV/AIDS are estimated to have risen to 12 % per year (Park, 2009). Although HIV and other immune compromised individuals are implicated in this disease, reports indicate that there are a few cases of *cryptococcal meningitis* unrelated to HIV infection (Mirza, 2003).

With the introduction of antiretroviral therapy (ART) rates in parts of the US decreased substantially from 23.6 per 1000 persons in 1993 to 1.6 per 1000 persons in the year 2000 (Mirza, 2003) despite ongoing debates about the best timing to start ART. Though the optimal timing to initiate ART is not clear, it is known that current ART regimens and adherence to treatment are capable of suppressing viremia and thereby create an environment that enhances the functions of the immune system of patients undergoing treatment (Bisson, 2008; Zolopa, 2009; Makadzange, 2010). Consequently, the effective provision of ART has caused significant reductions in morbidity and mortality associated with severe immune suppression and has led to a reduction in the incidence of *cryptococcal meningitis* in HIV/AIDS patients. Such reduction is observed more in countries where there

is early access to HIV care and prophylaxis for *cyptococcal meningitis* as well as early diagnosis during initial stages of the infection.

Current trends indicate that, most cases of *cyptococcal meningitis* found in Africa are among HIV-infected people with <100 cells/ $\mu$ l CD4 T cell count. Based on reported figures it is known that *cyptococcal meningitis* causes between 10-20 % deaths in Africa (French, 2002; Okongo, 1998; Park, 2009). Recently, a study in Malawi found *cyptococcal meningitis* to be the most common cause of meningitis disease with 40 % of cases from HIV-infected people. In West Africa, the disease is thought to be the most common opportunistic infection after mycobacteria. Data from West Africa are scanty due probably to a number of logistic problems and inefficiency with the health systems of the countries in this region, and as a result only a few of the cases in this region are reported here. Based on 2009 estimates 6 countries can be ranked from first to sixth in terms of total numbers of *cyptococcal meningitis* cases in West Africa. At the top of this hierarchy is Senegal, followed by Burkina Faso, Cote d’Ivoire, Mali, Niger and Ghana, with approximately 0.7-2.5 % patients with AIDS having cryptococcal infection.

Countries	Years of Study	Prevalence (%)	Study Place
Senegal (Soumare,2005)	2005	3.9 - 32.5	Infectious Diseases department of the Teaching Hospital of Fan
Burkina Faso (Ki-Zerbo,1996;Millogo,2004)	1996 to 2004	1.16 - 20.5	Internal medicine department of the Teaching Hospital of Ouagadougou
Cote D’Ivoire (Ouedraogo,2007)	2007	4.3 - 16.5	Internal medicine and Infectious Diseases departments of the Teaching Hospital of Coccody
Mali (Oumar,2008)	2008	8.3	Infectious Diseases of the Teaching Hospital of Point-g, Bamako
Niger (Seybou,2008)	2008	6.3	National Hospital of Niamey
Ghana (Frimpong,1998)	1998	0	Microbiology Laboratory of Kumasi

Note: Hierarchical list showing prevalence of *Cryptococcal meningitis* in West Africa obtained from different studies in this region.

Table 1. Prevalence of *Cryptococcal meningitis* in West Africa

### 3. Clinical & diagnostic profiles of *Cryptococcal meningitis*

#### 3.1 Clinical features

*Cryptococcal meningitis* is an insidious disease. Following infection, cryptococcus spread to other organs particularly the central nervous system (CNS) which is the main site in either immune competent or immune suppressed individuals. Most patients present with no symptoms and only report fever and mild headaches as a result of intracranial pressure. Reports from Burkina Faso showed that between 1996 and 1998, the major symptoms in patients with cryptococcal infection were headache and fever with 3 out of 7 patients having no neck stiffness (Millogo, 2004). However, patients who reported with the same disease in 2004 showed signs of neck stiffness, and headache. For patients with HIV/AIDS, the meningitis may spread rapidly to many organs. Records from Cote d'Ivoire showed that a number of hospitalized patients on admission presented with nonspecific severe symptoms that were associated with progression of *cryptococcal meningitis* disease including weight loss (44-62 %), chronic diarrhea (22-44.2 %), fever (50-85 %), chronic coughs (14 %), coma, convulsions and neck stiffness (24.4-85%) (Eholie, 2000). In Mali, 15 of 17 (88.2 %) cases with *cryptococcal meningitis* had signs of some abnormality while the remaining 2 had isolated fever. Overall, 14 of these patients had HIV-1 infection and their median CD4 T cell counts were <200 cells/ $\mu$ l (range 1-237 cells/ $\mu$ l). The CD4 T cell counts for the remaining 3 immune competent individuals were between 347 and 899 cells/ $\mu$ l (Minta, 2008). In Senegal, common symptoms reported were headache (86.7 %), fever (73.3 %), vomiting (66.7 %) and general weight loss (75.6 %). Most patients also presented with neurological signs including altered consciousness, seizures, motor deficits (paraplegia, flaccid hemi paresis and paraparesis), cranial nerve problems and coma at different stages of the disease. In 27 patients meningeal syndrome characterized by neck stiffness was followed by the presence of positive Kernig and/ or Bradzinski sign (Soumare, 2005a). There were no records for CD4 T cell counts of the patients studied here (Soumare, 2005b; 2005c). Data from Niger showed that all 8 HIV-1-infected patients with cryptococcosis had both fever and headache, 3 of 8 (37.5 %) had coma, and 1 (12.5 %) had seizures. The average CD4 T cell count for these patients was 41 cells/ $\mu$ l.

#### 3.2 Diagnostic features

Diagnosis of the disease is easy and requires no sophisticated methods or equipment. Specimens for laboratory diagnosis are collected based on the symptoms presented by the patient. Although most body fluids, including cerebro-spinal fluid (CSF), sputum, bronchoalveolar lavage (BAL), bronchial washings, biopsy tissues, prostatic fluid and blood, can be used for performing the test, the most common specimen used in many areas around the world is CSF. In West Africa, diagnosis is commonly performed by microscopic examination of CSF for yeast cells.

##### 3.2.1 Direct microscopy

The conventional method for laboratory diagnosis involves direct examination of CSF deposits by use of Indian ink/Nigrosin wet mount coloration to detect yeast cells. Direct microscopy of samples from HIV-infected individuals often yields positive results in 90% of cases (Desmet, 1989). It is more useful to perform blood culture for disseminated cases. To confirm diagnosis, CSF is cultured on Sabouraud agar plates for > 36 h. This allows cultures

to grow and the method can be utilized for evaluating disease burden by diluting aliquots of CSF and enumerating the number of colony-forming units for the fungal load in the specimen (Eholie, 2000; Ki-Zerbo, 1996; Millogo, 2004; Soumare, 2005c). With a little modification, the method can also be used for assessing efficacy of anticryptococcal regimens (Bicanic, 2009).

3.2.2 Serology

Some reports have indicated that, due to changes in the epidemiology of the infection, detection of small capsules of the antigen make recognition difficult with India ink staining (Bottone, 1986). A second method for diagnosing *C. meningitis* infection is therefore by use of latex agglutination test to detect cryptococcal polysaccharide capsular antigens of *C. neoformans*. This test can be performed on CSF and serum and there are commercially available kits (example Crypto-LA [International Biological Labs. Inc., Cranbury, N.J.], MYCO-Immune [American MicroScan, Mahwah, N.J.], and IMMY [Immuno-Mycologics, Inc., Norman, Okla], or CALAS [Meridian Diagnostics Inc., Cincinnati, Ohio]) with high sensitivity and specificity for carrying out this test. In most AIDS or other severely immune compromised patients, it is not useful to perform antibody detection tests.

Country	Different Studies	Diagnostic Methods		
		Culture of CSF	Serology	Direct Microscopy
Burkina Faso	Ki-Zerbo, 1996	+	-	+
	Millogo, 2004	+	-	+
Cote d'Ivoire	Eholie, 1997	-	+	+
	Eholie, 2000	+	+	+
	Eholie, 2004	+	+	+
	Ouedraogo, 2007	+	-	+
Mali	Oumar, 2008	-	-	+
	Minta, 2008	+	-	+
Senegal	Soumare, 2005a	+	+	+
	Soumare, 2005b	+	+	+
	Soumare, 2005c	+	+	+
Niger	Seybou, 2008	-	+	-
Ghana	Frimpong, 1998	+	-	+

Note: (+) is Used and (-) not Used

Table 2. Different Methods Used for Cryptococcus Diagnosis in West Africa

#### 4. Therapeutic aspects

Much progress has been made in the management of *Cryptococcal meningitis* in the developed world. For immune compromised patients with *Cryptococcal meningitis* three phases of therapy (induction for 2 weeks, consolidation for 8 weeks and maintenance for prolonged period) for receiving antifungal treatment have been suggested based on results from a clinical trial (van der Horst, 1997). Also, based on guidelines endorsed by the Infectious Diseases Society of America a higher dose of amphotericin B followed by fluconazole can be used to treat AIDS patients with cryptococcal meningitis. Of importance is that, although oral fluconazole is known to provide some initial relief from cryptococcal meningitis, it takes a longer duration to cleanse the cerebrospinal fluid of its fungal pathogens (Brouwer, 2004; Larsen, 1990; van der Horst, 1997).

It is now known that use of fluconazole alone, for treatment of the disease in AIDS patients is not enough, and that other approaches such as the use of amphotericin B combined with flucytosine, as well as increased immunological responses due to the use of antiretroviral drugs, are also required (Larsen, 1990). Thus, for immune suppressed patients with *cryptococcal meningitis*, treatment regimens include < 1.0 mg/kg/day amphotericin B deoxycholate (AmB) given intravenously plus 100 mg/kg/day flucytosine for 2 weeks followed by 400 mg oral Fluconazole for 8 weeks. In most countries in Africa however, due to a number of reasons including, cost, lengthy regulatory approval to import antifungal drugs, difficulty of administration and blood monitoring of amphotericin B-based therapy to avoid toxicity, fluconazole is used as primary therapy for the treatment of the disease (Bicanic 2009; Bicanic, 2005). Fluconazole causes fewer, less severe side effects, including skin rashes and liver enzyme abnormalities. Even with the use of fluconazole alone, problems with access to expert medical care and the management of complications of AIDS still exist in this region (Mwaba, 2001; Wertheimer, 2004). In most countries of West Africa fluconazole monotherapy was used.

Some reports have suggested that initial monotherapy with fluconazole led to relapse of HIV-associated cryptococcal meningitis. To prevent relapses, most doctors recommend that people who have had cryptococcal meningitis take fluconazole daily. Other drugs used include intravenous amphotericin B taken weekly or biweekly (Jackson, 2010).

Amphotericin B has many side effects, including kidney damage, high fever, low blood pressure, decreased numbers of red or white blood cells, nausea, vomiting, and chills. A newer formulation of the drug, in which the active compound is encased in a fatty substance, has been under study for a while and may have fewer side effects (Sharkey, 1996). However, more research is needed to assess the safety and effectiveness of this new form of amphotericin B. Flucytosin also may cause serious side effects, including decreased numbers of red or white blood cells, liver damage, nausea, diarrhoea, seizures, abdominal discomfort, or rash. In Mali treatment with amphotericin B and fluconazole injection is known to have had such side effects in 13 out of 17 patients (Oumar, 2008). Before the administration of amphotericin B, patients were injected with chlorpromazine (one hour before) and acetylsalicylic acid (30 min earlier). Then the infusions of amphotericin B were followed by an infusion of between 1.5-2 liters of 0.9% saline. This procedure was to reduce adverse effects associated with the use of amphotericin B (Oumar, 2008). In immune competent people, treatment is done using injectable amphotericin B alone, or followed by infusion of fluconazole treatment for some cases. In other cases, patients received amphotericin B in association with injectable ceftriaxon (Minta, 2008).

In Senegal fluconazole alone was the most commonly used antifungal in at least 93% of cases. It was used together with amphotericin B in one case (Soumare, 2005c). Here, the treatment strategy was the administration of fluconazole at 400 to 800 mg/day by intravenous infusion for 8 weeks, followed by a maintenance dose of 200 mg daily for a month. The maintenance treatment was however, continued until the CD4 count rose above 200 cells/ $\mu$ l for a period of 6 months (Soumare, 2005a). In Niger 3 out of 4 patients diagnosed in 2007 received monotherapy consisting of 400mg/day fluconazole (Seybou, 2008). The average duration of treatment was 25.2 days (range, 2-72 days). Although no HIV patients died during emergency periods, 165 cases (53%) were hospitalized and 147 patients were allowed to return home after the emergency care (47%) (Tanon, 2006). In a patient aged 66 years, cognitive functions declined partly from the 10th day. The delirium in a second patient aged 49 years, declined by the 10th day, and complete neurological recovery was observed at 3 months (Kouame, 2007). Overall, hospital stay period lasted for 25 days and between 1-50 days for those associated with cryptococcal meningitis. The severity of the prognosis was related to the combination of two or more opportunistic infections (Ouedraogo, 2007). In Burkina Faso, fluconazole was initially effective in two patients with a dose of 400mg/day, which was started on the eve of the death of a patient (Millogo, 2004).

The paucity of prospective data on the management of cryptococcal meningitis in patients without AIDS is the most challenging aspect of formulating treatment guidelines, but the principles of induction, consolidation, and maintenance were still applied. For patients with a predisposition to renal dysfunction a combination antifungal therapy with a lipid formulation of amphotericin B plus flucytosine was generally indicated.

## **5. Early diagnosis, Importance and challenges of ART initiation in the management of cryptococcal meningitis**

During HIV infection, because the CD4<sup>+</sup> T cells are the primary target of the virus, progressive loss of these cells leads to increasing immunodeficiency and risk of opportunistic diseases, progression to AIDS and ultimately death (O'Brien, 1996). The resurgence of HIV in resource poor settings in Africa and the complications associated with management of AIDS has led to a number of deaths attributable to cryptococcal meningitis. The good news is that reduction in CD4 cells can be reversed with effective antiretroviral therapy early in the course of infection and slow down its spread (Bisson, 2008). Despite this, it is important to note that often some proportion of patients who start therapy when their CD4 T cell counts are below 100 cells/ $\mu$ l are unable to gain restoration of their cells with ART and therefore pose additional challenges in treatment (Kelley, 2009). In addition to an increase in CD4 cell count, early initiation of therapy also increases general immune function, is cost-effective and facilitates the reduction in a number of clinical events, including lowering of incidence or risk of opportunistic infections. And although a number of guidelines are available for early initiation of ART in patients with AIDS-defining illnesses, the implementation of these guidelines in itself is a further challenge for resource-limited regions such as West Africa. Here, treatment poses additional financial burden because, under such guidelines ART will have to be provided for a large number of patients. Another concern is that, the use of ART comes with some complex challenges. Most notably is the possibility of developing immune reconstitution inflammatory syndrome (IRIS), a condition that occurs following rapid restoration of immune function after ART

Countries	Different Studies	Antifungal and adjuvant therapy						
		AmB	FCZ	KTZ	AmB ; ASA	FCZ; ASA	AmB ; FCZ	AmB ;FCZ ; SS CPMZ
Burkina Faso	Ki-Zerbo, 1996	-	+	+	-	-	-	-
	Millogo,2004	-	+	-	-	-	-	-
Cote D'Ivoire	Eholie,1997	+	-	-	-	-	-	-
	Eholie,2004	+	-	-	-	-	-	-
	Ouattara, 2007	-	-	-	-	+	-	-
	Ouedraogo, 2007	+	-	-	-	-	-	-
Mali	Oumar,2008	-	-	-	-	-	-	+
	Minta,2008	+	-	-	-	-	+	-
Senegal	Soumare, 2005a	-	+	-	-	-	+	-
	Soumare, 2005b	-	+	-	-	-	-	-
	N'diaye,2008	+	+	-	-	-	-	-
Niger	Seybou, 2008	-	+	-	-	-	-	-
Ghana	Frimpong , 1998	No Treatment as they didn't recovered the fungus						

(+) is Used and (-) not Used  
AmB : Amphotericin B ; FCZ : Fluconazol ; KTZ: Ketoconazole; CPMZ: Chlorpromazin;  
ASA: acetyl salicylic acid; SS: Saline solution

Table 3. Treatment Regimens used for Cryptococcus in West Africa

administration. In South Africa, cryptococcal reconstitution disease was associated with 6 of 22 deaths in a HIV-infected cohort within 3 months of starting ART (Bicanic, 2009; Lawn, 2005). Recent data also suggests potential drug interactions between nevirapine-based ART and high levels of fluconazole and the handling of any toxicities associated with this interaction may pose additional management difficulties in the West African context (Manosuthi, 2007).

## 6. The lethality of cryptococcal meningitis in West Africa

*Cryptococcal meningitis* is a disease that has a high chance of causing death. In West Africa, reported deaths associated with this disease are between 42 and 80% (Sow, 1998; Millogo, 2004; Eholie, 2000; Bissagnene, 1994; Ki-Zerbo, 1996; Soumare, 2005a; Kadjo, 2007; Oumar, 2008). The disease progresses to fatal states quickly. In 80% of cases, patients died before day 15 after hospitalization (Millogo, 2004; Seybou 2008). Such high mortality is correlated with an increased number of *Cryptococcal* pathogens similar to that seen with *Mycobacterium tuberculosis* (Eholié, 2000, Ouedraogo, 2007). One study noted that a lowered CSF glucose provides poor prognosis for *Cryptococcal meningitis* in West Africa (Ki-Zerbo, 1996). Pronounced immune deficiency and hematological abnormalities such as hyponatremia are also factors of poor prognosis (Eholié, 1997; Ki-Zerbo, 1996). Others noted that the lethality of the disease is significantly higher in patients with a CD4 T cell count below 20 cells/ $\mu$ l (Ki-Zerbo, 1996; Soumare, 2005a). Recent studies in the region indicate that the lethality of *Cryptococcal meningitis* is significantly associated with delay in diagnosis and initiation of appropriate treatment as well as non-compliance to drug therapy due to financial reasons (Eholié, 2000; Kadjo, 2007; Millogo, 2004; Ouattara, 2007; Oumar, 2008; Soumare, 2005b). The high lethality may also be due to inadequate treatment regimens used in the region (Oumar, 2008, Soumare, 2005a, Kadjo, 2007). The high fatality rate found in most countries of West Africa could be due to the fact that people consult with end-stage disease.

## 7. Conclusion

Impaired immunity associated with HIV infection has led to many complications. Effective introduction of anti-retroviral therapy has played a significant role in the reductions of Cryptococcosis in HIV/AIDS patients in most developed nations. The resurgence of HIV in developing countries has however, exposed many inadequacies in the management and control of cryptococcal meningitis in West Africa and elsewhere. Inadequate resources and an ineffective distribution of ART in this region could lead those with HIV to be more at risk of infection with *Cryptococcus* species. For those already having *Cryptococcus* disease, lack of early diagnosis offers an environment to progress to more fatal disease states.

Given that laboratory diagnosis of *Cryptococcal meningitis* is easy to perform and does not require extensive equipment, it is vital that the resources and capacity to perform this test is made available in centers of HIV care. An increasing number of studies have shown that relapses to initial treatment to cryptococcal disease is a possibility and can lead to further complications, including immune reconstitution inflammatory syndrome. Despite this knowledge, little is known of surveillance studies related to drug susceptibility to resistant cases of *Cryptococcal meningitis* in West Africa. More education at community and other grass root levels must be stepped up to increase awareness of the importance of early screening for *Cryptococcus* disease. In most resource-poor settings studied in West Africa,

the standard of care for HIV/AIDS patients with acute cryptococcal meningitis are dependent on availability of resources and access to anti-fungal drugs. Logically, as a first step, and if available it is necessary to sterilize the CSF of patients with amphotericin B, since this regimen is known to minimize resistance to fluconazole (Bicanic, 2006). As an alternative approach, it will be beneficial in this setting to give higher doses of fluconazole bearing in mind that better clinical and microbiological responses to fluconazole have been observed in some studies (Berry, 1992; Hossain, 2002). In addition, there is an urgent need for policy makers to step up capabilities for managing complications associated with HIV patients progressing to AIDS. Finally, given the impact of effective antiretroviral therapy in reducing HIV-associated morbidity and mortality it will be more supportive if in West Africa, governments and care-givers find easier alternative ways to reach patients with these drugs (ART) taking into consideration travel times to the health care centers which often deters patients from seeking care. Clearly, more work is needed in this region for the management of cryptococcal meningitis and includes a focus on effective diagnosis, therapeutic use of available medications and monitoring to avoid toxicity levels.

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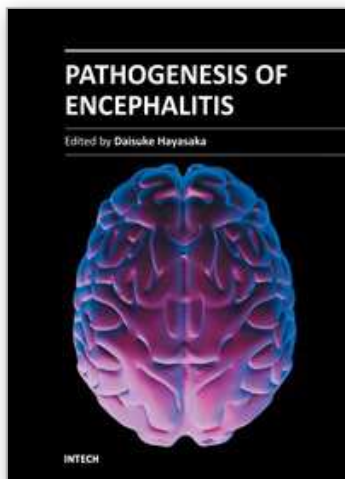
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## **Pathogenesis of Encephalitis**

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Many infectious agents, such as viruses, bacteria, and parasites, can cause inflammation of the central nervous system (CNS). Encephalitis is an inflammation of the brain parenchyma, which may result in a more advanced and serious disease meningoencephalitis. To establish accurate diagnosis and develop effective vaccines and drugs to overcome this disease, it is important to understand and elucidate the mechanism of its pathogenesis. This book, which is divided into four sections, provides comprehensive commentaries on encephalitis. The first section (6 chapters) covers diagnosis and clinical symptoms of encephalitis with some neurological disorders. The second section (5 chapters) reviews some virus infections with the outlines of inflammatory and chemokine responses. The third section (7 chapters) deals with the non-viral causative agents of encephalitis. The last section (4 chapters) discusses the experimental model of encephalitis. The different chapters of this book provide valuable and important information not only to the researchers, but also to the physician and health care workers.

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