University of Pharmacy, Yangon

CLINICAL EFFECTIVENESS AND SAFETY OF AMPHOTERICIN B WITH FLUCYTOSINE-FLUCONAZOLE THERAPY FOR CRYPTOCOCCAL MENINGITIS IN PATIENTS WITH HIV INFECTION

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LIST OF ABBREVIATIONS

ABCD	Amphotericin B colloidal dispersion
ABLC	Amphotericin B lipid complex
AmBd	Amphotericin B deoxycholate or conventional amphotericin
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine transaminase
AST	Aspartate transaminase
ART	Antiretroviral therapy
C-AMB	conventional amphotericin B
CD_4 count	CD_4+ T-lymphocyte count
CD	Cluster of Differentiation
CNS	Central Nervous System
CM	Cryptococcal meningitis
CSF	Cerebrospinal Fluid
DAIDS	Division of AIDS
HGB	Hemoglobin
HIV	Human immunodeficiency virus
ICP	Intracranial Pressure
IV	Intravenous
L-AMB	Liposomal amphotericin B
NAP	National AIDS Programme
NRS	Numerical rating scale
OD	Once a day
OI	Opportunistic infection
PLT	Platelet
PLHIV	People living with HIV
RCT	Randomized control trial
SD	Standard deviation
SGPT	Serum Glutamic Pyruvic Transaminase
SGOT	Serum Glutamic Oxaloacetic Transaminase

LIST OF ABBREVIATIONS

UNAIDS	Joint United Nations Programme on HIV/AIDS
WBC	White blood cells
WHO	World Health Organization

1. INTRODUCTION

1.1. Background Information

According to data of Joint United Nations Program on HIV/AIDS (UNAIDS, 2019), a population of 37.9 million of globally was living with HIV, and the annual number of deaths due to AIDS-related illnesses was 770,000 worldwide. Among them, 5.9 million people were from Asia and the Pacific region, with the estimated 200,000 AIDS-related deaths. In 2018, Myanmar had 240,000 adults and children living with HIV and there were about 7800 AIDS-related deaths (UNAIDS, 2019a). Although UNAIDS figured Myanmar high on its list of priorities as one of the six countries in Asia for the Global Fast Track Strategy to end HIV in 2030, there were still 11,000 adults and children newly infected with HIV in 2018 (UNAIDS, 2019b).

AIDS stands for acquired immune deficiency syndrome that develops as a result of advanced HIV infection which has destroyed the immune system and thus the body loses the ability to fight the organisms that cause diseases. The organisms take advantage of a weakened immune system, causing severe life-threatening opportunistic infections (OIs) (AIDSinfo, 2019b) that include Pneumocystis pneumonia (PCP), toxoplasma encephalitis, cytomegalovirus (CMV) retinitis, cryptococcal meningitis, tuberculosis, disseminated Mycobacterium avium complex (MAC) disease, and pneumococcal respiratory disease (AIDSinfo, 2019a).

Cryptococcal meningitis (CM) is the most common opportunistic fungal infection of the central nervous system (CNS) caused mostly by *Cryptococcus neoformans*. For people who have been exposed, the fungus remains largely latent in the body and most will never fall ill. But for those living with a compromised immune system, infection can spread from the lungs to the brain and spinal cord, causing meningitis (Rajasingham et al., 2017). It usually occurs in patients with advanced immunosuppression at CD4 count < 100/mm^3 (National AIDS Programme, 2017) and a major cause of morbidity and mortality especially in the developing world (WHO, 2019), with mortality within the first 3 months of diagnosis (Hevey et al., 2019). There were an estimated 220,000 cases of CM that occur among people with HIV/ AIDS worldwide each year, resulting in nearly 181,000 death (Rajasingham et al., 2017) and the disease account for 15% of AIDS-related deaths (Ponatshego et al., 2019).

Patients may present with headaches, fever, meningism, features of raised intracranial pressure, seizures (Heckmann & Bhigjee, 2014). In African and Vietnam trial, headache (100 %) was the most prominent clinical presentation which was followed by fever (77%), neck stiffness (73%), abnormal mental status (46.7%) and seizure (19.2%) (Day et al., 2013 & Molloy et al., 2018).

In WHO guideline (2018) for the management of cryptococcal disease, the preferred regimen is a short-course (one-week) induction regimen with amphotericin B deoxycholate and flucytosine followed by 1 week of fluconazole. It has been estimated that inductive treatment of Cryptococcal meningitis with flucytosine alone causes a prohibitive expense for low GDP nations (Shiri, 2019) and due to this reason, it is unavailable in all low and middle-income countries (Loyse et al., 2013). Thus, the treatment of cryptococcal meningitis in resource-limited settings is challenging (Molloy et al., 2018) and alternative options of two weeks amphotericin B deoxycholate plus fluconazole are used depending on drug availability (WHO, 2018). According to guidelines for clinical management of cryptococcosis in Myanmar, initiation of treatment is with Amphotericin plus Fluconazole for at least 2 weeks followed by consolidation with Fluconazole for 8 weeks followed by maintenance of Fluconazole until CD4 count rises to 200/mm^3 with ART (National AIDS Programme, 2017).

As a partner drug with amphotericin B, flucytosine was superior to fluconazole in cryptococcal meningitis in patients with HIV infection as one week of amphotericin B plus flucytosine was associated with the lowest mortality of 24.2% in ACTA (Advancing cryptococcal meningitis treatment for Africa) trial (Molloy et al., 2018). Moreover, clearance of cryptococci from the cerebrospinal fluid (CSF) was exponential and significantly faster with amphotericin B plus flucytosine than, amphotericin B plus fluconazole (Day et al., 2013).

Even where flucytosine (5FC) is available, it is often not administered because of overstated fears regarding toxicity (Loyse et al., 2013). The most serious drug-related adverse effect of 5FC is bone marrow suppression and hepatotoxicity (Vermes et al., 2000). In California's study, 5FC had be discontinued in over half of the patients because of cytopenia (Chuck & Sande, 1989). One patient in South Africa study also was discontinued 5FC because of thrombocytopenia on day-4 and the regimen was switched early to fluconazole (Bicanic et al., 2008). And also grade-4 neutropenia was recorded in 3.2% of the patients with 5FC (Molloy et al., 2018). But

in Thailand study, the treatment was well tolerated and there was no severe bone-marrow depression with 5FC (Brouwer et al., 2004).

Regarding amphotericin B Deoxycholate, its major drug-related adverse effects include nephrotoxicity and anemia (Bicanic et al., 2015). In Vietnam trial, Grade 3 and 4 anaemia were most prominent between amphotericin B plus flucytosine (35%) and amphotericin B plus fluconazole group (29%) (Day et al., 2013). Renal impairment occurs in nearly all patients treated with clinically significant doses of amphotericin. Fluconazole is relatively nontoxic, but reported to cause abnormalities in liver enzymes and very rarely, clinical hepatitis (Lampiris & Maddox, 2018).

Although WHO treatment guidelines recommend treatment regimen containing flucytosine as the preferred therapy, in clinical practice, treatment is highly variable due to drug costs, availability, and ability to monitor and manage drug-related toxicities (Perfect, 2010). A previous study was carried out in Mandalay for cryptococcal meningitis with fluconazole monotherapy by Than-Maung in 2006 and amphotericin B monotherapy by Myo-Thet-Naing in 2013 but the effectiveness and safety of amphotericin with flucytosine and fluconazole combination regime have not been studied in Myanmar. Thus, this study will provide information regarding the clinical effectiveness and safety of this treatment regimen for management of HIV-associated cryptococcal meningitis in Myanmar.

1.2. Justification

Cryptococcal meningitis is an AIDS-defining illness mostly caused by the fungus, *Cryptococcus neoformans*. In high-income countries, the use of amphotericin B in combination with a more expensive drug, flucytosine, is most effective for the management of cryptococcal meningitis; but access to flucytosine is severely limited in middle and low-income countries. In Myanmar, currently recommended regimen for cryptococcal meningitis are combination of amphotericin B with fluconazole. Although amphotericin plus flucytosine followed by fluconazole therapy is the currently preferred regimen in WHO treatment guidelines, it is not still commonly used in Myanmar clinical practice because of its limited availability. Therefore, the data regarding tolerability and clinical effectiveness of flucytosine are unavailable for Myanmar patients**.**

Although trials were carried out for investigating the effectiveness of flucytosine in the HIV population of Africa, the variability in drug response can occur

in Myanmar patients due to the racial and genetic differences and whether it is effective and safe for Myanmar people is a great curiosity question for clinicians and healthcare workers. In Myanmar, amphotericin plus flucytosine followed by fluconazole regimen will be supplied by National AIDS Program (NAP) and indicated in 2020. Thus, the documents for effectiveness and safety profile need to be established. This is the reason that the effectiveness and safety of amphotericin B with flucytosine and fluconazole combination therapy should be studied. From this study, it can provide information to physicians regarding the effectiveness as well as safety of those drugs in the management of cryptococcal meningitis in HIV patients.

2. LITERATURE REVIEW

2.1. Cryptococcosis

2.1.1. History

Cryptococcosis is an important cosmopolitan, infectious, mycotic disease of man and animals caused by the yeast, *Cryptococcus neoformans* which exists as saprobe in the environment. The disease is also known as Busse Buschke's disease, European blastomycosis or Torulosis. The disease was considered as sleeping disease in older days became an awakening giant in present era. Over a period of more than one hundred years ago, in 1894 *Cryptococcus neoformans* was discovered when this yeast was isolated independently from peach juice in Italy, by Sanfelice and from the tibial lesion of a patient in Germany by Busse (1894) and Buschke (1895), simultaneously. Sanfelice studied the pathogenicity of organisms in laboratory animals and gave name as *Saccharomyces neoformans* to the pathogen (cited by Nayak et al., 2010). In 1901, Jean-Paul Vuillemin, (Barnett, 2010) at Nancy University in France, named Busse's yeast *Cryptococcus hominis* and renamed Sanfelice's yeast *Cryptococcus neoformans* because neither yeast formed ascospores, as would be expected of a member of the genus Saccharomyces.

2.1.2. Epidemiology

Cryptococcus neoformans and *Cryptococcus gattii* are environmental, basidiomycetous yeasts. Unlike other pathogenic fungi, these yeast cells possess large polysaccharide capsules. Bird droppings (particularly pigeon droppings) enrich for the growth of *Cryptococcus neoformans* and serve as a reservoir of infection. The organism grows luxuriantly in pigeon excreta, but the birds are not infected. It is estimated that 1g of dry pigeon excreta may contain up to 50 million viable cells of *C. neoformans*.

It is isolated readily from dry pigeon feces, as well as trees, soil, and other sites. *Cryptococcus gattii* is less common and typically associated with trees in tropical areas. Both species cause cryptococcosis, which follows inhalation of desiccated yeast cells or possibly the smaller basidiospores (Brooks et al*.,* 2013). It can infect any organ in the body organs (e.g. skin, eyes, prostate), but has a predilection for the lung and the CNS. The lung is the usual portal of entry and symptoms range from

asymptomatic colonization to severe pneumonia. Meningitis is the most frequent manifestation of cryptococcosis (AIDSinfo, 2019a).

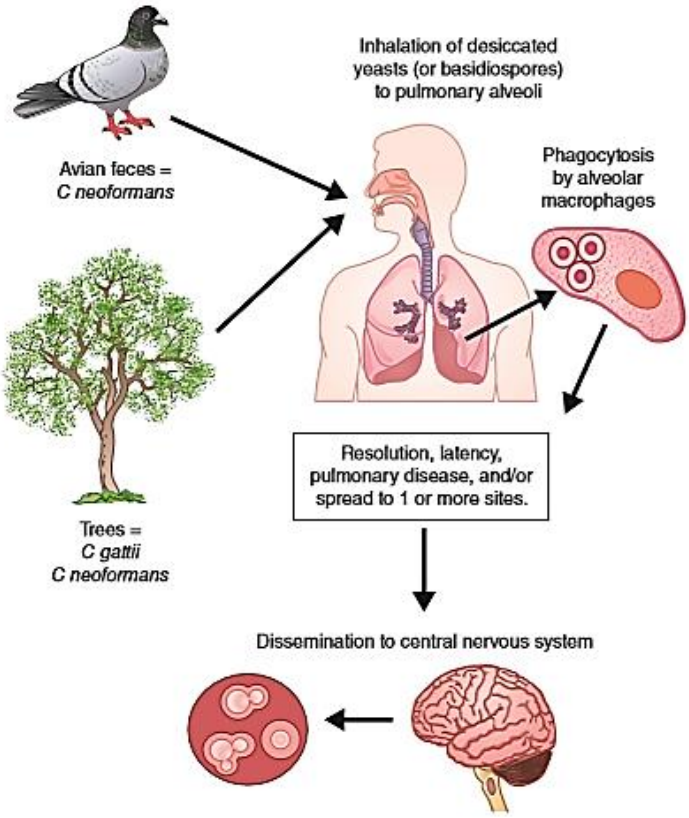


Figure (1) Natural history of cryptococcosis (Brooks et al., 2013)

Cryptococcus neoformans occurs in immunocompetent persons but more often in patients with HIV/AIDS, hematogenous malignancies, and other immunosuppressive conditions. In HIV-infected patients, the disease is associated with profound immunosuppression, usually occurring at CD_4 counts <100 cells/µl. There is a greater likelihood of involvement outside the CNS and relapse if antifungal therapy is discontinued prior to effective antiretroviral therapy (AIDSinfo, 2019a).

Overall, approximately one million new cases of cryptococcosis occur annually, and the mortality approaches 50%. More than 90% of these infections are caused by *C neoformans*. In sub-Saharan Africa, the epicenter of HIV/AIDS, *Cryptococcus neoformans* is the leading cause of meningitis with an estimated one million new cases and 600,000 deaths per year (Brooks et al., 2013).

2.1.3. Morphology and identification

In culture, Cryptococcus species produce whitish mucoid colonies within 2–3 days. Microscopically, in culture or clinical material, the spherical budding yeast cells (5–10 μm in diameter) are surrounded by a thick non-staining capsule. All species of Cryptococcus, including several nonpathogenic species, are encapsulated and possess urease. However, *C neoformans* and *C gattii* differ from nonpathogenic species by the abilities to grow at 37°C and the production of laccase, a phenol oxidase, which catalyzes the formation of melanin from appropriate phenolic substrates (eg, catecholamines). Both the capsule and laccase are well characterized virulence factors (Brooks et al., 2013).

There are four serotypes based on the capsular polysaccharide, glucuronoxylomannan (GXM) (Klatt, 2019). Capsular types A through D correspond to the variants C. neoformans var. grubii (A), C. neoformans var. gattii (B and C) and C. neoformans var. neoformans (D) (Warkentien, T & Crum-Cianflone, NF., 2010).

2.1.4. Pathogenesis

Cryptococcus is a basidiomycetous yeast that exists in the environment in the sexual form and produces hyphae with terminal basidiospores (chains of unbudded yeast) (Klatt, 2019). To enter the alveolar spaces of the lungs and establish pulmonary infection, an organism must produce viable forms smaller than 4 μm in diameter. The typical vegetative form of *C. neoformans* is the yeast form with a cell diameter of 2.5 to 10 μm (Nayak et al., 2010). When the 3μL basidiospores break off they become aerosolized and may be inhaled into the alveoli. Less commonly, the portal of entry is the gastrointestinal tract or the skin (Klatt, 2019). The organism remains dormant in the lungs until the immune system weakens and then reactivates and disseminate to the central nervous system, other body sites such as the skin, bone, joint, eye, heart, adrenals and prostate gland. (Nayak et al., 2010, Brooks et al., 2013). The inflammatory reaction is usually minimal or granulomatous (Brooks et al., 2013)

Cryptococcus may survive within human because of a polysaccharide capsule that allows it to evade phagocytosis. Capsular polysaccharides include galactoxylomannan as well as glucuronoxylomannan, and they impart resistance to phagocytosis. In addition, a phenol oxidase enzyme uses catecholamines as substrate to produce melanin, which accumulates in the cell wall, and synthesis of catecholamines

for neurotransmitters may predispose to involvement of the central nervous system (Klatt, 2019).

2.1.5. Clinical presentation

In HIV-infected patients, cryptococcosis commonly presents as a subacute meningitis or meningoencephalitis with fever, malaise, and headache. Classic meningeal symptoms and signs, such as neck stiffness and photophobia, occur in only one-quarter to one-third of patients. Some patients experience encephalopathic symptoms, such as lethargy, altered mentation, personality changes, and memory loss that are usually a result of increased intracranial pressure (AIDSinfo, 2019a). In African trial, headache (98.2 %) was the most prominent presentation which was followed by fever (52.9%), abnormal mental status (46.7%) and seizure (19.2%) (Molloy et al., 2018).

The findings in this study are comparable with those from studies from Myanmar. In the studies of Myo-Thet-Naing and Nyein-Chan-Win, headache was the most common presentation (100%). Other clinical parameters in order of decreasing frequency on admission were fever (58.70%), neck stiffness (45.65%) and impaired conscious level (13.04%) (Myo Thet Naing, 2013). In the study of Than-Maung, the most common clinical features are headache (97.87%), fever (85.11%), neck stiffness (63.83%), abnormal mental status (42.55%), convulsion (41.3%), focal neurological symptoms (14.89%) and papilledema (12.77%).

2.1.6. Diagnostic laboratory tests

A. Specimens, Microscopic Examination, and Culture

Specimens include cerebrospinal fluid, tissue, exudates, sputum, blood, cutaneous scrapings, and urine. Spinal fluid is centrifuged before microscopic examination and culture. For direct microscopy, specimens are often examined in wet mounts, both directly and after mixing with India ink, which delineates the capsule. Colonies develop within a few days on most media at room temperature or 37°C. Media with cycloheximide inhibit Cryptococcus and should be avoided. Cultures can be identified by growth at 37°C and detection of urease. Alternatively, on an appropriate diphenolic substrate, the phenol oxidase (or laccase) of *C neoformans* and *C gattii* produces melanin in the cell walls and colonies develop a brown pigment.

B. Serology

Tests for capsular antigen can be performed on cerebrospinal fluid, serum and urine. The latex slide agglutination test or enzyme immunoassay for cryptococcal antigen is positive in 90% of patients with cryptococcal meningitis. With effective treatment, the antigen titer drops—except in AIDS patients, who often maintain high antigen titers for long periods (Brooks et al., 2013).

2.1.7. Complications

Complications are common; raised intracranial pressure in the absence of ventricular dilatation may cause profound visual or hearing loss. Less commonly, patients may develop cognitive impairment and gait ataxia due to obstructive hydrocephalus with ventricular dilatation (Bicanic & Harrison, 2005).

(a) Raised intracranial pressure

The pathophysiology of elevated ICP in patients with cryptococcal meningitis is poorly understood and it is likely caused by several convergent factors. It has been postulated that it may be due to the outflow obstruction precipitated by aggregation of fungal polysaccharide accumulating in arachnoid villi and subarachnoid spaces thus providing the blockage of the channels for CSF drainage (Lee et al., 1996). Moreover, another possible important factor is cerebral oedema resulting from cytokine-induced inflammation and possibly osmotic effect by fungus-derived mannitol (Denning et al., 1991).

(b) Ophthalmologic Complications

The most severe ophthalmologic complication of cryptococcal meningitis is optic atrophy with resultant marked diminution of vision. This atrophy appears, at least in some patients, to be the result of direct invasion and destruction of the optic nerve by the cryptococci. The patients with most severe visual loss either had optic atrophy when first seen, or presented with minimal papilledema in relationship to CSF pressure (Okun & Butler, 1964).

2.1.8. Induction, consolidation and maintenance antifungal treatment regimens

Table 1. WHO 2018 Induction, consolidation and maintenance antifungal treatment regimens (WHO, 2018)

Induction (adults, adolescents and children)		
Preferred regimen	amphotericin B deoxycholate (1.0 mg/kg/day) and flucytosine (100 mg/kg/day, divided into four doses per day) (one week), followed by 1 week of fluconazole (1200 mg/day for adults, 12 mg/kg/day for children and adolescents, up to a maximum dose of 800mg daily)	Strong recommendation, moderate certainty evidence for adults, low-certainty evidence for children and adolescents
Alternative	Two weeks of fluconazole (1200 mg daily for adults, 12 mg/kg/day for children and adolescents) + flucytosine (100 mg/kg/day, divided into four doses per day)	strong recommendation, moderate-certainty evidence
Alternative	Two weeks of amphotericin B deoxycholate (1.0 mg/kg/day) + fluconazole (1200 mg daily for adults, 12 mg/kg/day for children and adolescents up to a maximum of 800 mg daily	strong recommendation, moderate-certainty evidence
Consolidation		
Consolidation	Fluconazole (800 mg daily for adults, 6–12 mg/kg/day for children and adolescents up to a maximum of 800 mg daily) for eight weeks following the induction phase	strong recommendation, low-certainty evidence
Maintenance (or secondary prophylaxis)		
Maintenance (or secondary prophylaxis)	Fluconazole (200 mg daily for adults, 6 mg/kg/day for adolescents and children)	strong recommendation, high-certainty evidence

In March 2018, WHO published "Guidelines for the Diagnosis, Prevention and Management of Cryptococcal Disease in HIV-Infected Adults, Adolescents and Children". This guideline recommends a short-course (one-week)

induction regimen with amphotericin B deoxycholate and flucytosine followed by 1 week of fluconazole is the preferred regimen. In low- and middle-income countries, due to limited availability of flucytosine, alternative options of two weeks amphotericin B deoxycholate plus fluconazole are used depending on drug availability (WHO, 2018). Although guidelines exist for the antifungal management of cryptococcal meningitis, recommendations are based on limited data from RCTs, and in clinical practice treatment is highly variable due to drug costs, availability, and ability to monitor and manage drug-related toxicities (Perfect, 2010).

Table 2. Myanmar Specialist hospital guidelines for clinical management of Cryptococcosis in patients with HIV (2019)

Initiation	IV Amphotericin 1 mg/kg plus Fluconazole 1200 mg IV/oral/ day for at least 2 weeks
Consolidation	Fluconazole 800 mg po od for 8 weeks
Maintenance	Fluconazole 200 mg OD until CD_4 count rises to 200/mm^3 with ART

Treatment for localized non-meningeal disease

Treatment with fluconazole 800 mg/day for two weeks followed by 400 mg/day for eight weeks followed by fluconazole 200-mg/day maintenance therapy is suggested based on expert opinion.

For optimal treatment of cryptococcoma, the following treatment regimen is suggested based on expert opinion: intravenous amphotericin B and oral flucytosine for at least six weeks, followed by consolidation and maintenance therapy with fluconazole (all doses similar to those used for cryptococcal meningitis). Corticosteroids or surgical intervention may be considered for intracranial lesions with evidence of mass effect (WHO, 2018).

Treatment for pregnant women

Amphotericin B therapy can be given to pregnant women with meningeal and non-meningeal disease. Exposure to flucytosine and fluconazole during pregnancy has been associated with an increased risk of birth defects in animal studies and some uncontrolled human studies. The use of flucytosine and fluconazole for treating cryptococcal disease in pregnant women should be evaluated on an individual basis, considering the benefits and potential harm (WHO, 2018).

2.1.9. Adjunctive corticosteroids in treating HIV-associated cryptococcal meningitis

Routine use of adjunctive corticosteroid therapy during the induction phase is not recommended in treating HIV-associated cryptococcal meningitis among adults, adolescents and children (strong recommendation, high-certainty evidence for adults and adolescents, moderate-certainty evidence for children) (WHO, 2018).

2.1.10. CSF fungal clearance

Thailand study revealed that clearance of Cryptococci from the CSF was exponential and was significantly faster with amphotericin B plus flucytosine than with amphotericin B alone (p=0·0006), amphotericin B plus fluconazole (p=0·02) (Brouwer *et al.,*2004). In Vietnam study, amphotericin B plus flucytosine was associated with significantly increased rates of yeast clearance from cerebrospinal fluid (−0.42 log10 colony-forming units [CFU] per milliliter per day vs. −0.31 and −0.32 log10 CFU per milliliter per day in groups 1 (amphotericin B) and 3 (Amphotericin B plus fluconazole), respectively; P<0.001 for both comparisons (Day et al., 2013). Largest ACTA trial confirmed that flucytosine as the partner drug given with amphotericin B was associated with more rapid clearance than fluconazole (Molloy et al., 2018).

2.1.11. Preventing, monitoring and managing antifungal toxicity

<u>Preventing, monitoring and managing antifungal amphotericin B toxicity</u>

Drug toxicity and side-effects from amphotericin B therapy, especially hypokalaemia, nephrotoxicity and anaemia, are barriers to optimal induction treatment, safe administration of amphotericin B should be given priority and may require referral to a centre with access to a minimum package of preventing, monitoring and managing toxicity (WHO, 2018).

Table 3. Minimum package for preventing, monitoring and managing amphotericin B toxicity (WHO, 2018).

Pre-emptive hydration and electrolyte supplementation	
Adults and adolescents	One litre of normal saline solution with 20 mEq of potassium chloride (KCl) over two hours before each controlled infusion of amphotericin B and one to two 8-mEq KCl tablets orally twice daily. An additional 8-mEq KCl tablet twice daily may

	be added during the second week. If available, magnesium supplementation should also be provided (two 250-mg tablets of magnesium trisilicate or glycerophosphate twice daily, or magnesium chloride 4 mEq twice daily).
Monitoring (adults, adolescents and children)	
Serum potassium	Baseline and 2–3 times weekly (especially in the second week of amphotericin B administration)
Serum creatinine	Baseline and 2–3 times weekly (especially in the second week of amphotericin B administration)
Haemoglobin	Baseline and weekly
Management (adults, adolescents and children)	
Hypokalaemia	If hypokalaemia is significant (K <3.3 mol/l), increase potassium supplementation to 40 mEq KCl by intravenous infusion and/or one to two 8-mEq KCl tablets orally three times daily. Monitor potassium daily.
Elevated creatinine	If creatinine increases by ≥2 fold from the baseline value, increase pre-hydration to 1 L every eight hours and consider temporarily omitting a dose of amphotericin B. Once creatinine improves, restart amphotericin B at 0.7 mg/ kg/day and consider alternate-day amphotericin B. If creatinine continues to rise, consider discontinuing amphotericin B and continuing with fluconazole at 1200 mg/ day, especially if seven doses of amphotericin have been received. Consider fluconazole dose adjustment if significant renal impairment. Monitor creatinine daily.
Severe anaemia	Transfusion should be undertaken if possible for severe amphotericin B–related anaemia (anaemia may also be a reason to discontinue amphotericin B prematurely in the second week of a planned two-week induction course of amphotericin B with fluconazole)
Additional notes:	

- Potassium replacement should not be given to people with pre-existing renal impairment or hyperkalaemia.
- Careful attention should be given to monitoring of intake and output of fluid and daily weight, especially among children.
- Flucytosine – because of concerns about bone marrow suppression, regular monitoring of full blood counts should be considered.
- The incidence of renal dysfunction and electrolyte disturbance is much less with liposomal amphotericin preparations, but renal function and electrolytes still need to be monitored

Managing fluconazole toxicity

-Renal insufficiency

If renal function decreases to 20-50 ml/min then reduce the dose by 50%

If renal function decreases to < 20 ml/min then reduce the dose by 25%

-Liver function abnormality (Perfect et al., 1992)

If during therapy, ALT (SGPT) from normal to 5x upper limit or form abnormal baseline increases by 150 then, if possible, stop fluconazole and switch to amphotericin.

-Drug Interactions

Fluconazole may increase levels of phenytoin, warfarin and sulfonylurea derivatives. If concomitant use of warfarin: check INR. If concomitant use of sulfonylurea derivatives there is risk of hypoglycemia, so check glucose levels more often.

Rifampicin will reduce the levels of fluconazole if the patient has been on it for > 2 weeks. Increase the dose of fluconazole by 50 %, in consolidation and maintenance phases.

Fluconazole is contraindicated in combination with cisapride and the new drug class of antihistamines such as terfenadine and astemizole (Molloy et al., 2018).

2.1.12. Safety

In ACTA trial, they randomly assigned HIV-infected adults with cryptococcal meningitis to receive an oral regimen (fluconazole [1200 mg per day] plus

flucytosine [100 mg per kilogram of body weight per day] for 2 weeks), 1 week of amphotericin B (1 mg per kilogram per day), or 2 weeks of amphotericin B (1 mg per kilogram per day). Each patient assigned to receive amphotericin B was also randomly assigned to receive fluconazole or flucytosine as a partner drug. Laboratory-defined side effects were less frequent in the oral-regimen group than in the 1-week or 2-week amphotericin B groups. Grade 4 anemia developed in 0.9% of patients in the oral-regimen group, 4.9% of patients in 1-week amphotericin B groups, and 8.8% of patients in the 2-week amphotericin B group. And also Grade 3 anemia developed in 4% of patients in the oral-regimen group, 8.9% of patients in 1-week amphotericin B groups, and 17.5% of patients in the 2-week amphotericin B group. A grade 3 or 4 increase in the serum creatinine level developed in 4.9% of patients in the oral-regimen group, 6.2% of patients in the 1-week amphotericin B groups, and 8.8% of patients in the 2-week amphotericin B groups. Grade 4 hypokalemia developed in only one patient, most likely because preemptive electrolyte replacement was provided for patients receiving amphotericin B.

Grade 4 neutropenia was recorded in 3.2% of the patients who were taking a regimen that included 2 weeks of flucytosine, in 0.9% of those taking 1 week of flucytosine, and in 1.3% of those taking a flucytosine free regimen. A grade 4 increase in the alanine aminotransferase level developed in only two patients, one of whom was taking fluconazole. Clinical adverse events were frequent with all regimens, which was reflective of the severe immunosuppression in this patient population.

As a partner drug with amphotericin, 1week amphotericin and flucytosine group develop Grade 3 and 4 anaemia of 8.8% and 24.56 % in 2 weeks amphotericin and fluconazole group. (Molloy et al., 2018).

In Vietnam trial, Grade 3 and 4 anaemia were most prominent between amphotericin B plus flucytosine (35%) and amphotericin B plus fluconazole group (29%). Grade 3 and 4 Neutropenia (9%) were similar between the two groups. 4% of amphotericin B plus flucytosine group develop Grade 3 and 4 thrombocytopenia with 3% in the fluconazole group. Grades 3 and 4 increase in aminotransferase level was 6% in flucytosine group and 14 % in fluconazole group (Day et al., 2013).

But in one cohort study of amphotericin B with fluconazole, none of the patients developed any serious Grade 3, 4 anaemia and elevated ALT level. Only 2 patients developed grade III hypokalemia and thrombocytopenia. And 7 patients

develop grade 3,4 neutropenia and 4 patients develop grade III elevated creatinine level. (Muzoora et al., 2011).

2.1.13. Mortality

In Africa trial, as a partner drug with amphotericin B, flucytosine was superior to fluconazole (71 deaths [31.1%] vs. 101 deaths [45.0%]; hazard ratio for death at 10 weeks, 0.62; 95% confidence interval [CI], 0.45 to 0.84; P = 0.002). One week of amphotericin B plus flucytosine was associated with the lowest 10-week mortality (24.2%; 95% CI, 16.2 to 32.1) (Molloy et al., 2018).

In Thailand study, the standard therapy for human immunodeficiency virus (HIV)–associated cryptococcal meningitis of amphotericin B (AmB; 0.7 mg/kg per day) plus flucytosine frequently takes 12 weeks to sterilize the cerebral spinal fluid, and acute mortality remains high. In this trial of AmB-based combination therapy, the10-week survival rate was 76%, the highest reported to date from Africa (Bicanic et al., 2008) At least two factors might explain high acute mortality: raised intracranial pressure and only moderately effective antifungal regimens, which frequently take more than 2 weeks to sterilize CSF. Mortality was 14% (nine/63) at 2 weeks and 22% (14/63) at 10 weeks. Elevated intracranial pressure was associated with death in 13 of 14 patients during step one. For the initial treatment of AIDS associated cryptococcal meningitis, the use of higher-dose amphotericin B plus flucytosine is associated with an increased rate of cerebrospinal fluid sterilization and decreased mortality at two weeks, as compared with regimens used in previous studies (Van Der Horst et al., 1997).In Vietnam study, combination therapy with flucytosine was associated with a reduced hazard of death, as compared with amphotericin B alone (hazard ratio, 0.56; 95% CI, 0.36 to 0.87; P = 0.01) or with amphotericin B plus fluconazole (hazard ratio, 0.55; 95% CI, 0.35 to 0.88; P = 0.01) (Day et al., 2013).

2.2.14. Timing of ART

Immediate ART initiation is not recommended for adults, adolescents and children living with HIV who have cryptococcal meningitis because of the risk of increased mortality and should be deferred by 4–6 weeks from the initiation of antifungal treatment (WHO, 2018).

3. AIM AND OBJECTIVES

3.1. Aim

To study the clinical effectiveness and safety of amphotericin B with flucytosine-fluconazole therapy for cryptococcal meningitis in patients with HIV infection.

3.2. Objectives

1. To find out the back-ground characteristics of patients with HIV-associated cryptococcal meningitis
2. To describe the clinical effectiveness of amphotericin B with flucytosine-fluconazole combination therapy by assessing clinical parameters at day 1, day 7 and day 14
3. To determine the severity of headache before and after treatment by numerical rating scale
4. To describe the clinical safety of amphotericin B with flucytosine-fluconazole combination therapy by assessing hematological and biochemical parameters by DAIDS grading at baseline, day 7 and day 14

3.3. Research Question

What will be the clinical effectiveness and safety of Amphotericin B with Flucytosine -Fluconazole combination therapy for cryptococcal meningitis in patients with HIV infection?

4. METHODOLOGY

4.1. Study Design

Hospital-based descriptive study

4.2. Study Site

1. Inpatient Departments of Specialist Hospital Waibargi (SHW)
2. Inpatient Departments of Specialist Hospital Mingalardon (SHM)
3. Inpatient Departments of Specialist Hospital Thakeyta (SHT)

4.3. Study Period

This study period will be conducted from October 2020 to September 2021.

4.4. Reference Population

Cryptococcal meningitis in patients with HIV infection

4.5. Study Population

Patients admitted to SHW, SHM and SHT with HIV-associated cryptococcal meningitis who will be treated with amphotericin + flucytosine + fluconazole induction regimen.

4.6. Selection Criteria

4.6.1. Inclusion criteria

1. Patients with HIV-associated cryptococcal meningitis, admitted to inpatient department of SHW, SHM and SHT during the study period
2. Patients of both sexes
3. Age above 14 years
4. Patients or caregivers who will give informed consent to participate in this study

4.6.2. Exclusion criteria

1. Pregnancy

4.6.3 Withdrawal criteria

1. On patient's request

4.7. Sample Size Determination and Sampling Procedure

4.7.1. Sample Size Determination

The sample size was calculated by using the following formula

$$n = \frac{z^2_{(1-\frac{\alpha}{2})}\ p\ (1\text{-}p)}{d^2}$$

Sample size for clinical safety,

Where,

p = Proportion of absence of grade III/IV anaemia in patients with HIV-associated cryptococcal meningitis infection after being treated with Amphotericin B, Flucytosine plus Fluconazole
= 0.83 (Molloy et al., 2018)

z = Standard normal deviate = 1.96 (95% CI)

d = Absolute precision = 0.14

n = minimal required sample size = 27

Sample size for clinical effectiveness,

Where,

p = Proportion of improvement of headache in patients with HIV-associated cryptococcal meningitis infection after being treated with Amphotericin, Flucytosine plus Fluconazole
= 0.8

z = Standard normal deviate = 1.96 (95% CI)

d = Absolute precision = 0.15

n = minimal required sample size = 27

So, the required sample size is 27.

4.7.2 Sampling Method

All patients admitted to the inpatient departments of SHW, SHM and SHT during the study period will be included.

4.8. Materials and Methods

After getting approval from medical superintendent, patients with HIV-associated cryptococcal meningitis admitted to inpatient departments of SHW, SHM and SHT will be studied. They will be given IV infusion of amphotericin B (1 mg/kg/day) and oral flucytosine (100 mg/kg) for one week followed by oral fluconazole (1200 mg/day) for one week according to the hospital standard treatment guideline chosen by the physician depends on patient's clinical condition. Before giving treatment, informed consent will be obtained.

All patients meeting the inclusion criteria will be studied under the supervision of experienced physicians. Baseline data for accessing clinical effectiveness such as fever, convulsion and abnormal mental status and for safety such as hematological and biochemical parameters (hemoglobin, neutrophil, platelet, ALT, AST, serum creatinine and serum potassium level) will be noted from medical charts. Hematological and biochemical parameters will be graded according to DAIDS grading. Assessment of headache and its severity will be done by numerical rating scale under the supervision of physician.

Seven days and fourteen days after treatment, clinical effectiveness parameters such as headache, fever, convulsion, abnormal mental status and death will be reassessed. Clinical safety concerning hematological and biochemical parameters like hemoglobin, neutrophil, platelet, ALT, AST, serum creatinine and serum potassium level will also be reassessed and graded according to DAIDS grading by reviewing from patient's medical charts at seven and fourteen days. With regard to severity of headache, it will be documented by using numerical rating scale at weekly intervals for two weeks. Clinical effectiveness parameters (headache, fever, convulsion, abnormal mental status and death) and hematological and biochemical parameters will be described. The results will be documented for data analysis.

4.9. Data Management and Analysis

Data will be collected by using pre-constructed pro forma. Following data collection and prior to data entry, all data will be carefully screened for accuracy.

Data entry will be done by using Microsoft Excel 2019. The data will be statistically analyzed by using computerized statistical software SPSS (Statistical Package for Social Science Version 21).

Data summarization for description will be done by showing frequency distribution tables and appropriate graphs. The parameters for clinical effectiveness and laboratory-defined adverse event gradings will be described by number, percentage in treatment group.

4.10. Operational Definitions

(1) HIV-seropositive patient

Patients who have been diagnosed as HIV infected patients by laboratory diagnostics tests in Myanmar. HIV testing strategies for HIV confirmation include three HIV antibody tests namely Determine (HIV-1/2) ICT, Uni-Gold (HIV) ICT and STAT-PAK (HIV 1/2) ICT (National AIDS Programme, 2017).

(2) Cryptococcal meningitis in patients with HIV infection

HIV-seropositive patient with symptoms and signs consistent with the diagnosis of cryptococcal meningitis and one or more of positive India ink test, positive cryptococcal antigen test in CSF.

(3) Clinical Effectiveness

Clinical effectiveness will be assessed by using these parameters such as headache, fever, convulsion, abnormal mental status and death.

(i) Severity of headache

Severity of headache is assessed by using Numerical rating scale (NRS). The NRS score range from zero to 10. Headache severity will be categorized according to the number given by patients for their headache. Headache will be categorized as no pain, mild, moderate, severe, and intolerable when scores are 0, 1-3, 4-6, 7-9, and 10. Headache will be evaluated by administration of a headache questionnaire at day-1, day-7 and day-14.

(ii) Fever

It is defined as rise in body temperature above 37 °C (98.6 °F) in the morning.

(iii) Convulsion

It is defined as a medical condition where body muscles contract and relax rapidly and repeatedly, resulting in uncontrolled actions of the body.

(iv) Abnormal mental status

It is defined as patients is somnolent, lethargy, disoriented and disruptions in perception and behavior.

(4) Clinical safety

Clinical safety will be assessed by laboratory defined adverse events. Adverse event is defined as any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product (Division of AIDS, 2017). Laboratory parameters (hematological and biochemical parameters) such as HGB, NEUT, PLT, ALT, AST, serum creatinine, serum potassium level will be graded according to DAIDS grading in appendix 3. Bone marrow suppression is defined as Grade 3 and 4 adverse events in one or more of anaemia, neutropenia and thrombocytopenia.

4.11. Ethical Considerations

The study will be hospital-based descriptive study regarding the clinical effectiveness and safety of amphotericin B with flucytosine-fluconazole combination therapy for treatment of HIV-associated cryptococcal meningitis. In this study, all patients according to selection criteria admitted to inpatient departments of SHW, SHM and SHT will be included. The participants eligible to the selection criteria will be invited to voluntary participation in the study and then explained in details about the study by the investigator with the information sheet of informed consent form (Part-I).

Only after they have understood the nature of study, objectives, methodology, procedure and duration, they can voluntarily take part in the study or they have right to refuse or withdraw at any time from the study without penalty of loss of benefit to which he or she would otherwise be entitled. If they agree, the written informed consent will be obtained by using informed consent form (Part-II) from all participants or from parents/relatives/next of kin if the patient could not provide the consent.

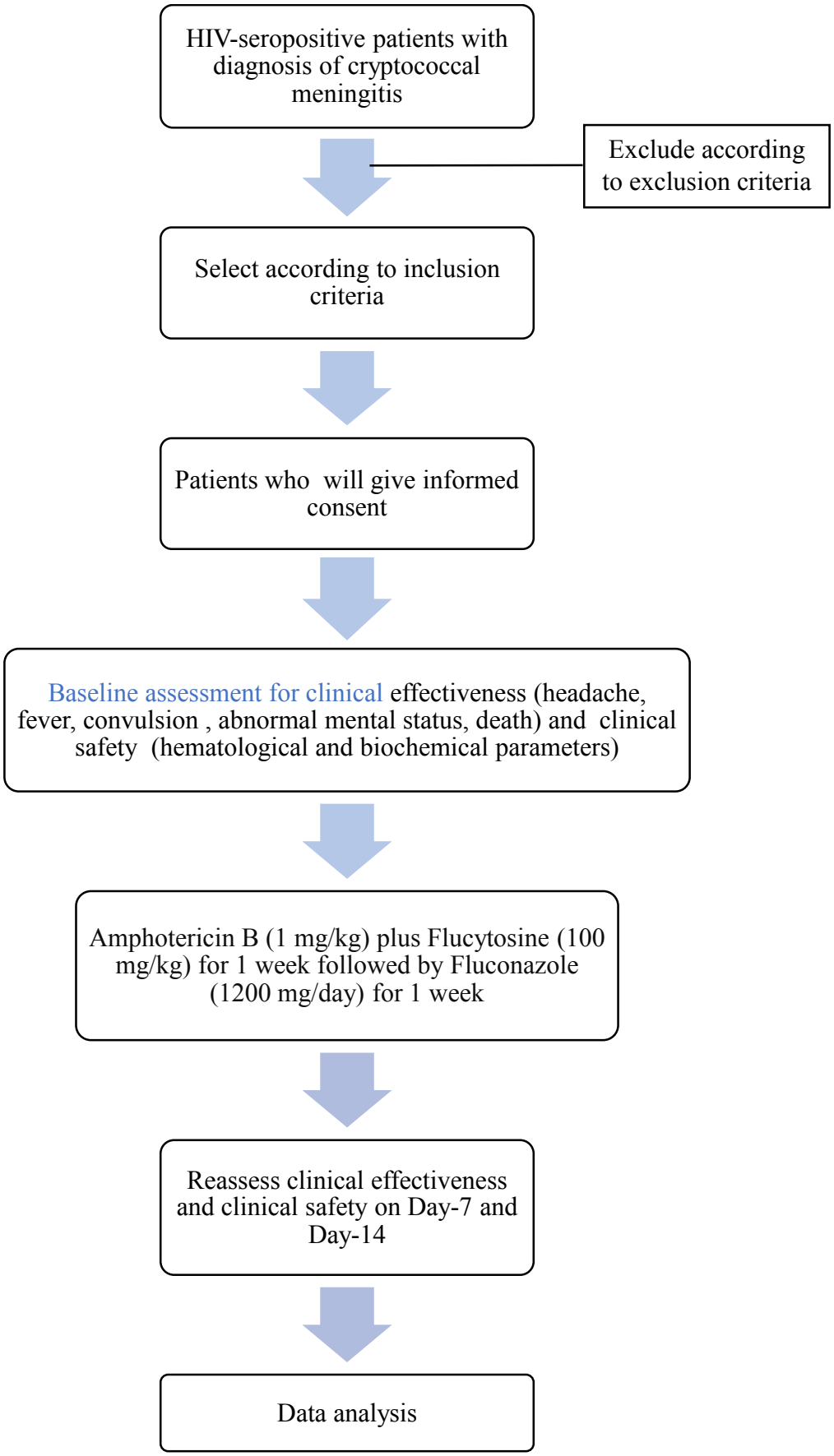
The study will be done under the supervision of a physician. The study will collect data under routine management. No new drugs will be administered and no treatment will be restricted for the purpose of thesis. The participants will be closely monitored throughout the research process. If any adverse reactions occur, the researcher will immediately inform to the physician and urgent treatment will be given and the necessary actions will be taken according to the standard treatment procedure.

The investigator will strictly maintain the rules of privacy and confidentiality. The name of patients will not be mentioned in this study. Only coded system will be used and research information will be kept by a password-protected file in the investigator's personal computer. All the personal information of the subject in Pro forma will be destroyed and the personal information in the investigator's personal computer will be deleted after the study period. The presentation on research data will be used in medical workshop, seminars and conference and the data will also be published for the academic purposes- only in thesis, papers and medical journals if necessary.

This study will follow the research guidelines of University of Pharmacy and laid out in the booklet - Manual for protocol and dissertation/ Thesis writing (2020). The research protocol will be summited and approved by the Ethic Review Committee (ERC) of University of Pharmacy.

It is the duty of the investigator to perform the research study according to the objectives, methodology and procedures approved by ERC of University of Pharmacy.

4.12. Algorithm



5. DUMMY TABLES

Table 4. Number of Cryptococcal meningitis in patients with HIV infection enrolled from individual specialist hospital

Hospital	Number (N)	Percentage (%)
Specialist hospital Waibargi		
Specialist hospital Mingalardon		
Specialist hospital Thakeyta		
Total		

Table 5. Distribution of age among study group of Cryptococcal meningitis in patients with HIV infection

Age (completed years)	Amphotericin B, Flucytosine plus Fluconazole group	
	Number	Percentage
≤ 20		
21-40		
>40		
Total		

Table 6. Distribution of gender among study group of Cryptococcal meningitis in patients with HIV infection

Gender	Amphotericin B, Flucytosine plus Fluconazole group	
	Number	Percentage
Male		
Female		
Total		

Table 7. Frequency distribution of headache among study group by Numerical rating Scale at day-1, day-7 and day-14

Days	Headache	Amphotericin B, Flucytosine plus Fluconazole group	
		Number	Percentage
day-1	No pain		
	Mild		
	Moderate		
	Severe		
	Intolerable		
Day-7	No pain		
	Mild		
	Moderate		
	Severe		
	Intolerable		
Day-14	No pain		
	Mild		
	Moderate		
	Severe		
	Intolerable		

Table 8. Clinical effectiveness of study group by assessing presence of headache, fever, convulsion, abnormal mental status and death at day-1, day-7 and day-14

Clinical parameters	**Amphotericin B, Flucytosine plus Fluconazole group**					
	Day 1		**Day 7**		**Day 14**	
	N	**%**	**N**	**%**	**N**	**%**
Headache						
Fever						
Convulsion						
Abnormal mental status						
Death						

Table 9. Laboratory-defined adverse events of amphotericin B, flucytosine and fluconazole at baseline and day-7 and day-14 by DAIDS grading

Days	**DAIDS Grading**	**Hematological parameters & Biochemical parameters**							**Total**
		Anaemia	**Neutropenia**	**Thrombocytopenia**	**Elevated ALT level**	**Elevated AST level**	**Hypokalemia**	**Hyper creatinemia**	
		N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	
Baseline	Grade 1								
	Grade 2								
	Grade 3								
	Grade 4								
Day-7	Grade 1								
	Grade 2								
	Grade 3								
	Grade 4								
Day-14	Grade 1								
	Grade 2								
	Grade 3								
	Grade 4								

Table 10. Proportion of patients with grade 3 and 4 adverse events of hematological parameters at baseline, day-7 and day-14

	Grade 3 and 4 adverse events	**Baseline**		**Day -7**		**Day -14**	
		N	**%**	**N**	**%**	**N**	**%**
Amphotericin B, Flucytosine plus Fluconazole group	Anaemia						
	Neutropenia						
	Thrombocytopenia						
Total							

Table 11. Proportion of patients who has bone marrow suppression at baseline, day-7 and day-14

Bone marrow suppression	**Baseline**		**Day -7**		**Day -14**	
	N	**%**	**N**	**%**	**N**	**%**
Amphotericin B, Flucytosine plus Fluconazole group						
Total						

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Annex 1. Pro forma

Title: Clinical effectiveness and safety of amphotericin B with flucytosine-fluconazole combination therapy for cryptococcal meningitis in patients with HIV infection.

Date ----------

Study site ----------

Code No ----------

I. Personal Identification

IPD Registration No. ----------

Name ----------

Age ----------

Gender ☐ Male ☐ Female

Date of Admission ----------

Occupation ----------

Address ----------

II. History taking and physical examination

Time of diagnosis of HIV ----------days ---------- months ---------- years

ART status Yes ☐

No ☐ Defaulter ☐

CD_4 count at admission -------- cells/μL

III. CSF Findings

Macroscopic

Colour ----------

Microscopic

Total cells count

R.B.C. ----------/cmm Neutrophil ----------%

W.B.C ----------/cmm Lymphocyte ----------%

CSF glucose ----------/mg/dL CSF protein ---------- mg%

India ink stain, Encapsulated yeast cell- seen ☐ not seen ☐

CSF opening pressure, cm H_2O ☐

Therapeutic lumbar puncture ☐ mL

CSF Crypto Ag Positive ☐ negative ☐

IV. Clinical diagnosis ----------

V. Treatment

Amphotericin B	1 mg/kg	1 week
Flucytosine	100 mg/kg	
Fluconazole	1200 mg/day	1 week

VI. Assessment of Headache (Headache Severity by Numerical rating scale)

Days	Numerical rating Scale				
	No pain 0	Mild 1-3	Moderate 4-6	Severe 7-9	Intolerable 10
Day 1					
Day 7					
Day 14					

VII. Assessment of Fever

Days	Temperature (morning)	
	Present	Absent
Day 1		
Day 7		
Day 14		

VIII. Assessment of Convulsion

Days	Convulsion	
	Present	Absent
Day 1		
Day 7		
Day 14		

IX. Assessment of Abnormal mental status

Days	Abnormal mental status	
	Present	Absent
Day 1		
Day 7		
Day 14		

X. Laboratory (hematological and biochemical) parameters

hematological and biochemical parameters	Baseline	Day-7	Day-14
HGB (g/dL)			
NEUT ($10^3/\mu L$)			
PLT ($10^3/\mu L$)			
ALT (U/L)			
AST (U/L)			
Serum creatinine (μmol/L)			
Potassium (mmol/L)			

Annex 2. Informed Consent Form (Myanmar and English)

သုတေသနလုပ်ငန်းတွင်ပါဝင်ရန် သဘောတူညီချက်ပေးသည့်ပုံစံ (မြန်မာ)

သုတေသနခေါင်းစဉ် - အိပ်(ချ်)အိုင်ဗွီ(HIV)ရောဂါပိုး ကူးစက်ခံရပြီး ခရစ်တိုကော့ကတ်မှို ရောဂါပိုးတစ်မျိုးကြောင့် ဦးနှောက်အမြှေးရောင်ရောဂါ ခံစားရသည့် လူနာများတွင် အမ်ဖိုထရေစင်ဘီ (Amphotericin B) နှင့်တွဲ၍ သုံးသည့် ဖလူဆိုက်တိုစင်း (Flucytosine) + ဖလူကိုနာဇော (Fluconazole) ပေါင်းစပ်ကုထုံး၏ လက်တွေ့တွင် ဘေးအန္တရာယ်ကင်းရှင်းမှု နှင့် အစွမ်းထက်မှု ကို လေ့လာခြင်း။

သုတေသနပြုလုပ်သူ - ဒေါ်ဇင်ဝင်းမေ

သုတေသနအဖွဲ့အစည်း - ဆေးဝါးဗေဒဌာန၊ ဆေးဝါးတက္ကသိုလ်၊ ရန်ကုန်။

အပိုင်း (က) သုတေသနနှင့်ပတ်သက်၍ရှင်းလင်းတင် ပြချက်

(၁) နိဒါန်း

ဤသုတေသနကို ဆေးဝါးတက္ကသိုလ်၊ရန်ကုန် ဆေးဝါးဗေဒဌာနမှ ဆေးလက်တွေ့ဆေးဝါးသိပ္ပံ ဘွဲ့လွန်ပထမနှစ်ကျောင်းသူ ကျွန်မ ဒေါ်ဇင်ဝင်းမေ မှ လုပ်ဆောင်မည် ဖြစ်ပါသည်။ ယခုသုတေသနကို ဆေးလက်တွေ့ဆေးဝါးသိပ္ပံမဟာဘွဲ့ အတွက် ဆောင်ရွက်ခြင်း ဖြစ်ပါသည်။

ယခုသုတေသနသည် အထူးကုဆေးရုံ(ဝေဘာဂီ)၊ အထူးကုဆေးရုံ (မင်္ဂလာဒုံ) နှင့် အထူးကုဆေးရုံ (သာကေတ) တွင် အိပ်(ချ်)အိုင်ဗွီရောဂါပိုး ကူးစက်ခံရပြီး ခရစ်တိုကော့ကတ်မှိုရောဂါပိုး တစ်မျိုးကြောင့် ဦးနှောက်အမြှေးရောင်ရောဂါ ခံစားရသည့်လူနာများတွင် သုံးမည့် ဆေး ၃မျိုး (Amphotericin B, Flucytosine နှင့် Fluconazole) ၏ လက်တွေ့တွင် ဘေးအန္တရာယ် ကင်းရှင်းမှုနှင့် အစွမ်းထက်မှုကို လေ့လာခြင်းဖြစ်ပါသည်။ ကျွန်မသည် ဤသုတေသန လုပ်ငန်းအကြောင်း ရှင်းပြအသိပေးပြီး သင့်အားပါဝင်ရန် ဖိတ်ခေါ်ပါသည်။ သုတေသန လုပ်ငန်းတွင် ပါဝင်ခြင်း၊ မပါဝင်ခြင်းကို

ယခုဆုံးဖြတ်ပေးစရာမလိုပါ။ သင်ဆုံးဖြတ်ချက်မချခင် ဤသုတေသနလုပ်ငန်းနှင့် ပတ်သက်၍ သင်ခံစားရသမျှ မည်သူမဆို ပြောပိုင်ခွင့် ရှိပါသည်။ ကျွန်မပြောသော စကားများထဲမှနားမလည်သောစကားလုံးများရှိပါကလည်းကျွန်မအားချက်ချင်းမေးနိုင်ပါသ ည်။ကျွန်မအားလုံးရှင်းပြပါမည်။အကယ်၍ နောက်ပိုင်းတွင် မေးစရာမေးခွန်းများ ပေါ်လာပါက ကျွန်မ (သို့မဟုတ်) သင့်အားကုသနေသော ဆရာဝန်ထံမေးမြန်းနိုင်ပါသည်။ ဤသုတေသနမှ လက်တွေ့တွင် ပို၍ ဘေးအန္တရာယ် ကင်းရှင်းပြီး အစွမ်းထက်သည့် ဆေးဝါးများ၏ အချက်အလက်များကို ရရှိနိုင်သဖြင့် နောင်တွင် ဆရာဝန်များအနေဖြင့် ပိုမိုကောင်းမွန်သော ကုသမှုကိုပေးနိုင်ရန် ရည်ရွယ်ပါသည်။

(၂) ရည်ရွယ်ချက်

ယခုသုတေသနလုပ်ငန်း၏ ရည်ရွယ်ချက်မှာ အထူးကုဆေးရုံ(ဝေဘာဂီ)၊ အထူးကုဆေးရုံ (မင်္ဂလာဒုံ) နှင့် အထူးကုဆေးရုံ (သာကေတ) တွင် အိပ်(ချ်)အိုင်ဗီရောဂါပိုး ကူးစက်ခံရပြီး ခရစ်တိုကော့ကတ်မို့ ရောဂါပိုးတစ်မျိုးကြောင့် ဦးနှောက်အမြှေးရောင်ရောဂါ ခံစားရသည့် လူနာများတွင် အမ်ဖိုထရေစင်ဘီ (Amphotericin B) နှင့်တွဲ၍ သုံးသည့် ဖလူဆိုက်တိုစင်း (Flucytosine) + ဖလူကိုနာဇော (Fluconazole)ပေါင်းစပ်ကုထုံး ၏ လက်တွေ့တွင် ဘေးအန္တရာယ်ကင်းရှင်းမှု နှင့် အစွမ်းထက်မှု ကို လေ့လာရန် ဖြစ်ပါသည်။ ယခု အသုံးပြုမည့် ဆေးဝါးများကို ၂၀၁၈ ခုနှစ်တွင် ကမ္ဘာ့ကျန်းမာရေးဌာန၏ အိပ်(ချ်)အိုင်ဗီရောဂါပိုး ကူးစက်ခံရသော လူကြီး၊လူငယ် နှင့် ကလေးများ၏ ခရစ်တိုကော့ကတ်မို့ရောဂါကို ရောဂါရှာဖွေခြင်း၊ ကာကွယ်ခြင်း၊ ကုသခြင်းလမ်းညွှန်တွင် အတည်ပြုပြီး ဖြစ်ပါသည်။

(၃) သုတေသန ပြုလုပ်မည့်လုပ်ဆောင်ချက်

ဤသုတေသနသည်ဆေးရုံအခြေပြုလေ့လာသောသုတေသန ဖြစ်ပါသည်။

(၄) သုတေသနတွင်ပါဝင်မည့်သူရွေးချယ်ခြင်း

အထူးကုဆေးရုံ(ဝေဘာဂီ)၊ အထူးကုဆေးရုံ (မင်္ဂလာဒုံ) နှင့် အထူးကုဆေးရုံ (သာကေတ)တို့တွင် အိပ်(ချ်)အိုင်ဗီရောဂါပိုး ကူးစက်ခံရပြီး ခရစ်တိုကော့ကတ်မှိုရောဂါပိုး တစ်မျိုးကြောင့် ဦးနှောက်အမြှေးရောင်ရောဂါ ခံစားရသည့် လူနာများမှ သုတေသနဆိုင်ရာ ရွေးချယ်မှု သတ်မှတ်စံနှုန်းဖြင့် ကိုက်ညီသူများ ပါဝင်မည်ဖြစ်ပါသည်။

(၅) ဆန္ဒအလျောက်ပါဝင်ခြင်း

ဤသုတေသနတွင် ပါဝင်ရန်မှာ ပါဝင်သူ၏ သဘောဆန္ဒ အလျောက် ဖြစ်ပါသည်။ ဤသုတေသန လုပ်ငန်း တွင် ပါဝင်ပြီးသည့် နောက်ပိုင်း နှုတ်ထွက်လိုပါကလည်း ဆန္ဒအလျောက် အချိန်မရွေး နှုတ်ထွက်နိုင်ပါသည်။ ဤသို့ နှုတ်ထွက်ပါကလည်း ရောဂါကုသမှုတွင် ပြောင်းလဲသွားခြင်း ရှိမည်မဟုတ်ပါ။ မရှင်းလင်းသည့် အချက်အလက်များနှင့် အခြားသိရှိလိုသည်များကို သုတေသနပြုလုပ်သူ (သို့မဟုတ်) ဘာသာရပ်ဆိုင်ရာ ကျွမ်းကျင်သူ တစ်ဦးဦးထံ မေးမြန်းနိုင်ပါသည်။

(၆)သုတေသနပြုလုပ်မည့်အစီအစဉ်

သုတေသနတွင်ပါဝင်သူ၏ ခွင့်ပြုချက် ရရှိပြီးမှ ဤလုပ်ငန်းကို စတင်ပါမည်။ သုတေသနပြုလုပ်မည့်သူသည် ယခုသုတေသနအမျိုးအစား၊ ပါဝင်မည့် လုပ်ဆောင်ချက်များ၊ အကျိုးကျေးဇူးနှင့် အန္တရာယ်တို့ကိုသုတေပြုသူမှ သုတေသနပြုရာတွင် ပါဝင်သူအား သဘာတူညီချက်ရရှိနိုင်ရန် ရှင်းလင်းပြောပြပါမည်။ ရောဂါဖြစ်စဉ် ရာဇဝင်ကောက်ယူခြင်း၊ စမ်းသပ်စစ်ဆေးခြင်းနှင့် ဓာတ်ခွဲရလာဒ်အဖြေများကို အထူးကုဆေးရုံ(ဝေဘာဂီ)၊ အထူးကုဆေးရုံ (မင်္ဂလာဒုံ) နှင့် အထူးကုဆေးရုံ (သာကေတ) ၏အတွင်းလူနာဌာနရှိလူနာ၏ ဆေးဘက်ဆိုင်ရာ အချက်အလက်ကတ်ပြား မှကောက်ယူမည်ဖြစ်ပြီး လူနာ၏ ခေါင်းကိုက်မှု အခြေအနေ အကဲဖြတ်မှုမှတ်တမ်းကို သမားတော်၏ ကြီးကြပ်မှုအောက်တွင် လုပ်ဆောင်

မည် ဖြစ်ပါသည်။ သုတေသနကာလ(၂)ပါတ်အတွင်းတွင် သုတေသနပြုသူသည် ပါဝင်သူ၏ ကျန်းမာရေးအခြေအနေ အကဲဖြတ်မှုမှတ်တမ်း နှင့် ဓာတ်ခွဲရလာဒ်အဖြေများ ကောက်ယူမှု၊ လူနာ၏ခေါင်းကိုက်မှုအခြေအနေ အကဲဖြတ်မှုကို သမားတော်၏ကြီးကြပ်မှုအောက်တွင် တစ်ပါတ်တစ်ကြိမ် ဆောင်ရွက်မည် ဖြစ်ပါသည်။

(၇)ကြာမြင့်ချိန်

သုတေသနပြုလုပ်မည့်သူနှင့် သုတေသနတွင်ပါဝင်မည့်သူသည်စုစုပေါင်း (၃) ကြိမ်တွေ့ဆုံရပါမည်။ ပထမအကြိမ်အနေဖြင့် သုတေသနဆိုင်ရာ အချက်အလက် ကောက်ယူခြင်း၊ ခေါင်းကိုက်မှုအခြေအနေ မှတ်တမ်းကောက်ယူခြင်း အတွက် ခန့်မှန်းချိန် ၁၅ မိနစ်မှမိနစ် ၃၀ ကြာမြင့်မည်ဖြစ်ပါသည်။ ကျန်သော (၂)ကြိမ်တွင်သုတေသနပြုသူသည် သမားတော်၏ လမ်းညွှန်မှုအောက်တွင် လူနာ၏ ခေါင်းကိုက်မှုအခြေအနေ မှတ်တမ်းကို ကောက်ယူမည် ဖြစ်ပါသည်။ ၎င်းတစ်ခုချင်းစီ အတွက် ခန့်မှန်းခြေ ၅ မိနစ်မှ ၁၀ မိနစ်အထိ ကြာမြင့်မည် ဖြစ်ပါသည်။ သုတေသနပြုသူနှင့်၃ ကြိမ်တွေ့ဆုံပြီးချိန်တွင် သုတေသနတွင် ပါဝင်ခြင်း ပြီးဆုံးပါမည်။ သုတေသနအတွက် စုစုပေါင်း ကြာချိန်မှာ မိနစ် ၅၀ ဖြစ်ပါသည်။

(၈) ကြုံတွေ့နိုင်သည့်ဘေးထွက်ဆိုးကျိုး

ဤသုတေသနသည် လူနာ၏ ဆေးဘက်ဆိုင်ရာအချက်အလက် ကတ်ပြားမှ အချက်အလက်များကိုသာကောက်ယူမည်ဖြစ်ပါသဖြင့် ဤသုတေသနကြောင့် လူနာအ ပေါ်တွင် ဘေးထွက်ဆိုးကျိုး ဖြစ်ပေါ်စေမည်မဟုတ်ပါ။ အကယ်၍ သုတေသနပြုလုပ်နေစဉ် ပုံမှန်မဟုတ်သော ဘေးထွက်ဆိုးကျိုးများဖြစ်ပေါ်ပါကသုတေသနပြုသူသည်သမားတော်သို့ ချက်ချင်း အကြောင်းကြားပြီး လိုအပ်သောကုသမှု ခံယူနိုင်ရန် ဆောင်ရွက်ပေးပါမည်။

(၉) ကြံ့တွေ့နိုင်သည့် အန္တရာယ်

ဤသုတေသနသည်ပုံမှန်ကုသမှုပေးနေသောကုသမှုလုပ်ငန်း တွင် ဝင်ရောက်ဆောင်ရွက်မည်ဖြစ်သောကြောင့် ဘေးအန္တရာယ်မှာ အလွန်နည်းပါးပါသည်။

(၁၀) ကြံ့တွေ့နိုင်သည့်အဆင်မပြေမှု

သုတေသနလုပ်ငန်းဆောင်ရွက်ချိန်တွင် မေးခွန်းများဖြေဆိုရခြင်းကြောင့် စိတ်မသက်သာမှုအနည်းငယ်ကြံ့တွေ့ရနိုင်ပါသည်။

(၁၁) အကျိုးကျေးဇူးများ

ဤသုတေသနရလာဒ်များသည် အိပ်(ချ်)အိုင်ဗီရောဂါပိုး ကူးစက်ခံရပြီး ခရစ်တိုကော့ကတ်မှုရောဂါပိုးတစ်မျိုးကြောင့် ဦးနှောက်အမြှေးရောင်ရောဂါ ခံစားရသည့် လူနာများ ရောဂါပျောက်ကင်းနိုင်ခြင်း အပြင် ဆရာဝန်များ၊ ကျန်းမာရေးဝန်ထမ်းများ အတွက်များစွာ အကျိုးရှိစေမည် ဖြစ်ပါသည်။

(၁၂) အကျိုးခံစားခွင့်

ဤသုတေသနတွင်ပါဝင်သည့်အတွက် ပါဝင်သူများအနေဖြင့် ငွေကြေး (သို့မဟုတ်) လက်ဆောင်များ ခံစားခွင့် မရှိပါ။သို့သော် သုတေသနတွင် ပါဝင်သည့်အတွက် ပိုမိုထိရောက်သော ကုသမှုရရှိမည်ဖြစ်ပါသည်။

(၁၃) သုတေသနရလာဒ်များ လျှို့ဝှက်ထိန်းသိမ်းထားရှိမှု

သုတေသနပြုလုပ်သူက သုတေသနတွင် ပါဝင်သူ တစ်ဦးချင်းစီ၏ ကိုယ်ရေးအချက်အလက်များကို မည်သည့် ပုဂ္ဂိုလ်၊ အုပ်စု၊ အဖွဲ့အစည်း ထံသို့မှ ခွင့်ပြုချက်မရဘဲ ပေါက်ကြားမှု မရှိအောင် ထိန်းသိမ်းရန် တာဝန် ယူပါသည်။ သုတေသနဆိုင်ရာ အချက်အလက်များ နှင့် လူနာ၏ရောဂါစစ်ဆေးမှု အဖြေတို့ကို စနစ်တကျလျှို့ဝှက်ထိန်းသိမ်း

ထားမည်ဖြစ်ပါသည်။ သုတေသန တွင် ပါဝင်သူ ၏ ကိုယ်ရေးအချက်အလက်များ ကို အမည် ဖော်ပြခြင်း မပြုဘဲ ကုဒ်နံပါတ်စနစ် ဖြင့် မိမိ၏ ကိုယ်ပိုင် ကွန်ပြူတာတွင် သေချာစွာ သိမ်းဆည်းထားမည် ဖြစ်ပါသည်။စာရွက်စာတမ်းများ၊ ကွန်ပျူတာမှတ်တမ်းဖိုင် များကိုလည်း သုတေသနပြုသူနှင့် သုတေသန ကြီးကြပ်သူတို့မှအပ အခြား မသက်ဆိုင်သည့်သူများ ကြည့်ရှုခြင်း၊ ထုတ်ယူခြင်း မပြုနိုင်အောင် လုံခြုံသည့်နည်း ဖြင့် သိမ်းဆည်းမည် ဖြစ်ပါသည်။

(၁၄) သုတေသနရလဒ်အချက်အလက်များကိုဖြန့်ဝေခြင်း

သုတေသနမှ ရရှိသော အဖြေရလာဒ်များကို ဆေးပညာဆိုင်ရာ အလုပ်ရုံဆွေးနွေးပွဲများ၊ ကျန်းမာရေးအသိပညာ နှီးနှောဖလှယ်ပွဲများ၊ ဆေးပညာဆိုင်ရာ ညီလာခံများနှင့် အချက်အလက်များကို ဆေးပညာဆိုင်ရာ သုတေသနစာတမ်းနှင့် ဂျာနယ်များတွင် အသုံးပြုရန်လိုအပ်မှသာ အသုံးပြုပါမည်။ ပါဝင်သူများ၏ ကိုယ်ပိုင် အချက်အလက်များကို ဖော်ပြမည်မဟုတ်ပါ။

(၁၅) သုတေသနတွင် ပါဝင်ရန်ငြင်းဆိုခွင့် (သို့မဟုတ်) သုတေသနမှ နှုတ်ထွက်ခွင့်

သုတေသနလုပ်ငန်းတွင် သင်၏ ပါဝင်မှုသည် မိမိသဘောဆန္ဒအရသာဖြစ်ပြီး သုတေသနတွင်မပါဝင်လိုလျှင် အစပိုင်းတွင် ငြင်းပယ်နိုင်သည့်အပြင် သုတေသနတွင် ပါဝင်နေစဉ် အချိန်မရွေး ငြင်းပယ်နိုင် (သို့မဟုတ်) နှုတ်ထွက်နိုင်ပါသည်။ ထိုသို့ ပြုလုပ်ခြင်းကြောင့် ပုံမှန်ရောဂါ ဆက်လက်ကုသမှုကိုထိခိုက်စေမည်မဟုတ်ပါ။

(၁၆) ဆက်သွယ်စုံစမ်းရန်

ဤသုတေသနနှင့် ပက်သတ်၍ သင့်အနေဖြင့် မေးမြန်းစရာများ မရှင်းလင်းသည်များရှိပါက ယခုမေးနိုင်ပါသည်။ နောက်မှမေးလိုလျှင်လည်း အောက်ပါ လိပ်စာအတိုင်း စုံစမ်းမေးမြန်းနိုင်ပါသည်။

ဒေါ်ဇင်ဝင်းမေ

ပထမနှစ်၊ ဆေးလက်တွေ့ဆေးဝါးမဟာသိပ္ပံသင်တန်း

ဆေးဘက်ကျွမ်းကျင် (၂) (ဆေးဝါး)၊ အထူးကုဆေးရုံ (သာကေတ)၊ ရန်ကုန်မြို့ ။

ဖုန်းနံပါတ် - ၀၉၉၇၅၅၀၆၉၈၄

အပိုင်း (ခ) သဘောတူညီချက်

(၁) ကျွန်တော်/ကျွန်မသည် အိပ်(ချ်)အိုင်ဗီရောဂါပိုး ကူးစက်ခံရပြီး ခရစ်တိုကော့ကတ်မှိုရောဂါပိုးတစ်မျိုး ကြောင့်ဖြစ်သော ဦးနှောက်အမြှေးရောင်ရောဂါ တွင်သုံးသော ဆေးများ၏ သုတေသနအတွက် ပါဝင်ရန် ဖိတ်ကြားခြင်း ခံရပါသည်။ ၎င်းသုတေသနတွင် လူနာ၏ ခေါင်းကိုက်မှုအခြေအနေ မှတ်တမ်းကို ကောက်ယူရန် သုတေသနပြုလုပ်သူနှင့်(၃)ကြိမ်တွေ့ဆုံရမည်ဖြစ်ကြောင်းသိရှိပါသည်။ ဤသုတေသနသည် ပုံမှန်လုပ်ရိုးလုပ်စဉ်ကုသမှုလုပ်ငန်းအတွင်းတွင်ဝင်ရောက်ဆောင်ရွက်မည်ဖြစ်ပြီးဤသုတေသနကြောင့် ဘေးအန္တရာယ် မဖြစ်ကြောင်း ပြောပြထားပြီးဖြစ်ပါသည်။

(၂) သုတေသနနှင့်ဆိုင်သော လိုအပ်သော ကျန်းမာရေးစောင့်ရှောက်မှု မှအပ အခြားမည်သည့်ခံစားခွင့်မှ မရှိကြောင်းကို သိရှိပြီးဖြစ်သည်။ ကျွန်တော်/ကျွန်မသည် သုတေသနပြုသူအမည် ၊ ဆက်သွယ်ရန် ဖုန်းနံပါတ်နှင့်လိပ်စာ တို့ကိုလည်းသိရှိပြီး ဖြစ်သည်။

(၃) အထက်ဖော်ပြပါ စာပိုဒ်များမှ အကြောင်းအရာများအားလုံးကို ကောင်းစွာ အသေးစိတ် ဖတ်ရှုပြီး (သို့) ဖတ်ကြားပြသည်ကို နားထောင်ပြီးဖြစ်ပါသည်။ နားမလည်ပါက ပြန်လည် မေးမြန်းခွင့်ရရှိပြီး မည်သည့်မေးခွန်းမဆို ကျေနပ်သည်အထိ သုတေသနပြုမှ ပြန်လည် ဖြေဆိုပြီးဖြစ်ပါသည်။ ကောင်းစွာနားလည် သဘောပေါက်ပါသည်။

(၄) မိမိကိုယ်တိုင် သဘောဆန္ဒအရ သုတေသနတွင် ပါဝင်မည်ဖြစ်ပြီး အချိန်မရွေး သုတေသနမှ မိမိဆန္ဒအလျောက် နုတ်ထွက်နိုင်ကြောင်း နားလည်ပါသည်။

ဆေးပညာအကျိုးအလို့ငှာ သုတေသန၏ တွေ့ရှိချက်အဖြေများကိုလည်း ကိုယ်ရေးကိုယ်တာဖော်ပြချက်မပါဘဲ ထုတ်ဖော်တင်ပြရန်အတွက် သဘောတူခွင့်ပြုပါသည်။

သုတေသနတွင်ပါဝင်မည့်သူ၏ လက်မှတ် ----------

သုတေသနတွင်ပါဝင်မည့်သူ၏ အမည် ----------

သုတေသနတွင်ပါဝင်မည့်သူ၏ လိပ်စာ ----------

နှင့် ဖုန်းနံပါတ် (ရှိလျှင်) ----------

ရက်စွဲ (လ၊ ရက်၊ နှစ်) ----------

<u>အကယ်၍စာမတတ်ပါက</u>

ယခုသုတေသနတွင် ပါဝင်မည့်သူ (လူနာ)အား ကျွန်ုပ်၏ ရှေ့မှောက်တွင် သဘောတူညီချက် များကို တိတိကျကျ ရှင်းလင်းဖတ်ပြပြီး ဖြစ်ပါသည်။ ပါဝင်သူက မရှင်းလင်းသည်များကိုလည်း မေးမြန်းခွင့် ရရှိပါသည်။ ထိုသူသည် ဆန္ဒအလျောက် သဘောတူညီချက်ကို လွတ်လပ်စွာ ပေးခြင်းဖြစ်ကြောင်း အတည်ပြုပါသည်။

ပါဝင်သူ လက်ဝဲလက်မလက်ဗွေပုံစံ

	အသိသက်သေလက်မှတ် ----------
	အသိသက်သေအမည် ----------
	ရက်စွဲ (လ၊ ရက်၊ နှစ်) ----------
	အသိသက်သေနေရပ်လိပ်စာ ----------

ကျွန်ုပ်သည် ဤသုတေသနတွင် ပါဝင်မည့်သူအား သဘောတူညီချက်များကို တိတိကျကျ ရှင်းလင်းဖတ်ပြပြီးဖြစ်ပါသည်။ ပါဝင်သူကမရှင်းလင်းသည်များကိုလည်း မေးမြန်းခွင့် ရရှိပါသည်။ ထိုသူသည် မိမိဆန္ဒအလျောက် သဘောတူညီချက်ကို လွတ်လပ်စွာ ပေးခြင်းဖြစ်ကြောင်း အတည်ပြုပါသည်။

သုတေသနပြုသူ၏ လက်မှတ် ----------

သုတေသနပြုသူ၏အမည် ----------

ရက်စွဲ (လ၊ ရက်၊ နှစ်) ----------

သဘောတူညီချက် မိတ္တူတစ်စောင်ကို သုတေသနတွင် ပါဝင်သူမည့်သူအား ပေးအပ်ပြီး ဖြစ်ပါသည်။ ----------

အပိုင်း(ခ) သဘောတူညီချက် (ကိုယ်တိုင်သဘောတူညီချက်မပေးနိုင်သူများအတွက်)

(၁) ကျွန်တော်/ ကျွန်မသည် သုတေသနတွင်ပါဝင်သူ၏---------- တော်စပ်သူဖြစ်ပါသည်။

(၂) ကျွန်တော်/ကျွန်မ ၏ ဆွေမျိုး/သားသမီး သည် အိပ်(ချ်)အိုင်ဗီရောဂါပိုး ကူးစက်ခံရပြီး ခရစ်တိုကော့ကတ်မှိုရောဂါပိုးတစ်မျိုး ကြောင့်ဖြစ်သော ဦးနှောက်အမြှေးရောင်ရောဂါ တွင်သုံးသော ဆေးများ၏ သုတေသနအတွက် ပါဝင်ရန် ဖိတ်ကြားခြင်း ခံရပါသည်။ ၎င်းသုတေသနတွင် လူနာ၏ ခေါင်းကိုက်မှုအခြေအနေမှတ်တမ်းကို ကောက်ယူရန် သုတေသနပြုလုပ်သူနှင့်(၃)ကြိမ်တွေ့ဆုံရမည်ဖြစ်ကြောင်းသိရှိပါသည်။ ဤသုတေသနသည် ပုံမှန်လုပ်ရိုးလုပ်စဉ်ကုသမှုလုပ်ငန်းအတွင်းတွင်ဝင်ရောက်ဆောင်ရွက်မည်ဖြစ်ပြီးသုတေသန ကြောင့် ဘေးအန္တရာယ် မဖြစ်ကြောင်း ပြောပြထားပြီးဖြစ်ပါသည်။

(၃) ကျွန်တော်/ကျွန်မအပါအဝင် ကျွန်တော်/ကျွန်မ၏ ဆွေမျိုး/သားသမီးအတွက် သုတေသနနှင့်ဆိုင်သော လိုအပ်သော ကျန်းမာရေးစောင့်ရှောက်မှုမှအပ အခြားမည်သည့် ခံစားခွင့်မှ မရှိကြောင်းကို သိရှိပြီးဖြစ်သည်။ ကျွန်တော်/ကျွန်မသည် သုတေသနပြုသူအမည်၊ ဆက်သွယ်ရန် ဖုန်းနံပါတ် နှင့်လိပ်စာတို့ကိုလည်း သိရှိပြီး ဖြစ်သည်။

(၄) အထက်ဖော်ပြပါစာပိုဒ်များမှအကြောင်းအရာများအားလုံးကိုကောင်းစွာ အသေးစိတ် ဖတ်ရှုပြီး (သို့) ဖတ်ကြားပြသည်ကို နားထောင်ပြီးဖြစ်ပါသည်။ နားမလည်ပါက

ပြန်လည်မေးမြန်း ခွင့်ရရှိပြီး မည်သည့်မေးခွန်းမဆို ကျေနပ်သည် အထိ သုတေသနပြုသူမှ ပြန်လည်ဖြေဆိုပြီး ဖြစ်ပါသည်။ ကောင်းစွာ နားလည် သဘောပေါက်ပါသည်။

(၅) ကျွန်တော်/ကျွန်မ၏ ဆွေမျိုး/သားသမီး အား သုတေသနတွင် ပါဝင်ရန် ၎င်းကိုယ်စား မိမိသဘော ဆန္ဒအလျောက် သဘောတူညီချက်ကို လွတ်လွတ်လပ်လပ်ပေးခြင်းဖြစ်ကြောင်း အတည်ပြုပါသည်။ ဤသုတေသနမှ မိမိသဘောဆန္ဒအလျောက် အချိန်မရွေး နှုတ်ထွက် နိုင်ကြောင်း နားလည်ပါသည်။

ပါဝင်သူ၏အမည် ----------

ပါဝင်သူ၏ဆွေမျိုး/မိဘလက်မှတ် ----------

ပါဝင်သူ၏ဆွေမျိုး/မိဘအမည် ----------

ရက်စွဲ (လ၊ ရက်၊ နှစ်) ----------

<u>အကယ်၍စာမတတ်ပါက</u>

ယခုသုတေသနတွင် ပါဝင်မည့်သူ (လူနာ)အား ကျွန်ုပ်၏ ရှေ့မှောက်တွင် သဘောတူညီချက် များကို တိတိကျကျ ရှင်းလင်းဖတ်ပြပြီး ဖြစ်ပါသည်။ ပါဝင်သူက မရှင်းလင်းသည်များကိုလည်း မေးမြန်းခွင့် ရရှိပါသည်။ ထိုသူသည် ဆန္ဒအလျောက် သဘောတူညီချက်ကို လွတ်လပ်စွာ ပေးခြင်းဖြစ်ကြောင်း အတည်ပြုပါသည်။

ပါဝင်သူဆွေမျိုး၏လက်ဝဲလက်မလက်ဗွေပုံစံ

	အသိသက်သေလက်မှတ် ----------
	အသိသက်သေအမည် ----------
	ရက်စွဲ (လ၊ ရက်၊ နှစ်) ----------

အသိသက်သေနေရပ်လိပ်စာ ----------

အပိုင်း(ခ) သဘောတူညီချက် (သုတေသနပြုသူအတွက်)

ကျွန်ုပ်သည် ဤသုတေသနတွင် ပါဝင်မည့်သူအား သဘောတူညီချက်များကို တိတိကျကျ ရှင်းလင်းဖတ်ပြပြီးဖြစ်ပါသည်။ ပါဝင်သူက မရှင်းလင်းသည်များကိုလည်း မေးမြန်းခွင့် ရရှိပါသည်။ ထိုသူသည် မိမိဆန္ဒအလျောက် သဘောတူညီချက်ကို လွတ်လပ်စွာ ပေးခြင်းဖြစ်ကြောင်း အတည်ပြုပါသည်။

သုတေသနပြုသူ၏ လက်မှတ် ----------

သုတေသနပြုသူ၏အမည် ----------

ရက်စွဲ (လ၊ ရက်၊ နှစ်) ----------

သဘောတူညီချက် မိတ္တူတစ်စောင်ကို သုတေသနတွင် ပါဝင်သူမည့်သူ/ ပါဝင်မည့်သူ၏ မိဘ/အုပ်ထိန်းသူ/အနီးစပ်ဆုံးဆွေမျိုး အား ပေးအပ်ပြီးဖြစ်ပါသည်။----------

Informed Consent Form (English)

Title - Clinical effectiveness and safety of amphotericin B with flucytosine-fluconazole combination therapy for cryptococcal meningitis in patients with HIV infection

Principal investigator - Daw Zin Win May

Organization - Department of pharmacology, University of Pharmacy, Yangon.

PART I. Information sheet

(1) Introduction

The investigator is Daw Zin Win May, first year master student of clinical pharmacy, who will perform this study to fulfill the degree of M. Pharm. (Clinical Pharmacy), University of Pharmacy, Yangon.

The present study will identify clinical effectiveness and safety of amphotericin B, flucytosine and fluconazole in HIV-associated cryptococcal meningitis patients at specialist hospital Waibargi, Mingalardon and Thakeyta, Yangon. I am going to give you information about this research and invite you to participate in it. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research. There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask me or any general practitioner who you are consulting. As it will provide information for better and safer drugs, clinicians will be able to give better treatments.

(2) Purpose

The aim of this research is to study the clinical effectiveness and safety of amphotericin B with flucytosine-fluconazole combination therapy for cryptococcal meningitis in patients with HIV infection at specialist hospital Waibarigi, Minglardon and Thakeyta, Yangon. The drugs used in this research are approved by WHO 2018 guideline for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children.

(3) Type of research intervention

This research is hospital based descriptive study.

(4) Participants selection

All HIV patients with cryptococcal meningitis attending at specialist hospital Waibarigi, Minglardon and Thakeyta who would meet the eligibility criteria will be invited to participate in this study.

(5) Voluntary participation

The participation in this research is entirely voluntary. It is participant's choice whether to participate or not, all the services received at these hospitals will continue and nothing will change. The participants can stop participating even if agreed earlier. The participant is free to refuse to take part or withdraw at any time without interfering management plan.

(6) Protocol and Procedures

After getting informed consent from those participants, the research will be done. Participants will be explained about the type and procedure of the research to get the informed consent from the participant. History taking and physical examination and laboratory results will be noted from medical charts of specialist hospital Waibargi and Mingalardon, and assessment of headache and its severity will be done under the supervision of physician. During the 2 weeks, researcher will access patient headache condition weekly for two weeks.

(7) Duration

Researcher and participants will encounter three times. For the first time, it will be taken about 15-30 minutes for the participants who give informed consent to fill pro forma. For the rest of the times, researcher will note down the patient's condition and assess headache severity by numerical rating scale under the supervision of physician. Each of the time will takes approximately 5-10 minutes. After three times, the involvement of participants in this study will finish. The total duration of the study will be about 50 minutes.

(8) Side effects

There is no side effect at all in conducting this research because only the data recorded from patient's medical chart will be collected and accessed. If any unusual side effects occur during the research, the researcher will immediately inform

to the physician and urgent treatment will be given and the necessary actions will be taken according to the standard treatment procedure.

(9) Risks

The risks will be minimal because it will be done under the routine treatment.

(10) Discomforts

There will be a little psychological discomfort in answering questions during the research process.

(11) Benefits

By conducting this study, HIV patients with cryptococcal meningitis as well as clinicians and health care workers will get benefits from the results of the study.

(12) Incentives

There will be no financial or material incentives for the participants. But the patient will get more effective treatment by participating in this research.

(13) Confidentiality

The researcher will not reveal the patient's identity and information to any person, group or institution without permission. Strict confidentiality will be maintained upon research data and results concerning the patients All the information and confidential data of the subjects will be maintained and kept confidentially by using coding system in the investigator's personal computer. Both documentaries and computerized information will be kept safely and no one apart from the researcher with the exception of research colleagues and supervisors will have authorized to assess them.

(14) Sharing the result

The results of the study will be shared only in medical workshop, seminars and conference and the data will only be published for the academic purposes-

only in thesis, papers and medical journals if necessary. The confidential information of the participants will not be shared.

(15) Right to refuse or withdraw

Your participation is completely voluntary and you can refuse or withdraw to participate in the study at any time. It has no effect on receiving optimal treatment for the participants.

(16) Whom to contact

If you have any questions you may ask me now or later, even after the study has been started. If you wish to ask questions later, you may contact any of the following:

Daw Zin Win May
First Year, M.Pharm. (Clinical Pharmacy)
Pharmacist, Specialist Hospital (Thaketa), Yangon.
Phone number: 09975506984

PART II. Certificate of Consent

(a) Certificate of Consent (Adult)

1. I have been invited to participate in research of drugs used for treatment of cryptococcal meningitis. I understand that it will involve answering questions for headache condition and two follow-up visits. I have been informed that the study will be done under the routine management and the risks are minimal.
2. I am aware that there may be no charges or incentives for participation in this research. I have been provided with the name, contact phone number and address of the researcher who I can easily contact to.
3. I have read the foregoing information, or it has been read to me. I have been given opportunity to ask question about the study and have been answered to my satisfaction. I understand very well about the research.
4. I consent voluntarily to participate as a participant in this research and understand that I have the right to withdraw from the research at any time without in anyway affecting my medical care.

Name of Participant ----------

Signature of Participant ----------

Date (day/ month / year) ----------

If illiterate,

A literate witness must sign (if possible, this person should be selected by the participant and should not have no connection to the research team). Participants who are illiterate should include their thumb print as well.

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Name of witness _____ and Thumb print of participant

Signature of witness _____

Date (Day/month/ year) _____

I have accurately read or witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Name of Researcher _____

Signature of Researcher _____

Date (Day/month/year) _____

A copy of this Informed Consent Form has been provided to participant _____

(initialed by the researcher)

For children under 18 years of age and un-autonomous persons

1. I have been invited to have my child/patient participate in research of drugs used for treatment of cryptococcal meningitis. I understand that it will involve my child/patient answering questions for headache condition and two follow-up visits. I have been informed that the study will be under the routine management and the risks are minimal.
2. I am aware that there may be no charges or incentives to either myself or my child/patient personally for participation in this research. I have been provided

with the name, contact phone number and address of the researcher who I can easily contact to.

3. I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I understand very well about the research.
4. I consent voluntarily for my child/patient to participate as a participant in this study and understand that I have the right to withdraw my child/patient from the study at any time without in any way affecting either my patient's or my own medical care.

Name of Participant ----------

Signature of parent or guardian ----------

Name of parent or guardian ----------

Date (day/ month / year) ----------

If illiterate,

A literate witness must sign (if possible, this person should be selected by the participant and should not have no connection to the research team). participant's parent/guardian who are illiterate should include their thumb print as well.

I have witnessed the accurate reading of the consent form to the potential participant's parent/guardian, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Name of witness _____and Thumb print of parent/guardian

Signature of witness _____

Date (Day/month/year) _____

I have accurately read or witnessed the accurate reading of the consent form to the parent or guardian of the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Name of Researcher _____

Signature of Researcher _____

Date (Day/month/year) _____

A copy of this Informed Consent Form has been provided to the parents/guardian/relatives/next of kin of participant _____

(initialed by the researcher)

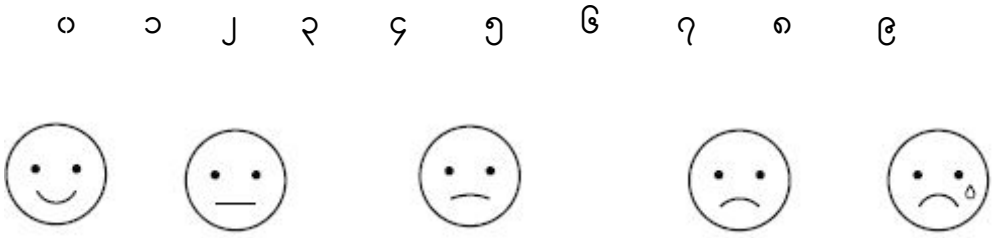
Annex 3. Scale

Headache severity assessment

A numeric rating scale (NRS) is used to assess the severity of headache. The NRS score range from zero to 10. Headache severity will be categorized according to the number given by patients for their headache. Headache will be categorized as no pain, mild, moderate, severe, and intolerable when scores are 0, 1-3, 4-6, 7-9, and 10. Headache will be evaluated by administration of a headache questionnaire at the time of admission and during the follow up.

ခေါင်းကိုက်ရာတွင်နာကျင်မှုအဆင့်နှုန်းသတ်မှတ်ချက် မှတ်တမ်း

သင်၏နာကျင်မှုအဆင့်ကို သိသာစေရန် အသင့်တော်ဆုံး နံပါတ်တစ်ခုကိုရွေးချယ်ပေးပါ။



Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life-threatening
Hemoglobin, Low (g/dL) ≥ 13 years of age (male only)	10.0 - 10.9	9.0 - 10.0	7.0 - 9.0	< 7.0
≥ 13 years of age (female only)	9.5 - 10.4	8.5 - 9.5	6.5 -8.5	< 6.5
Absolute Neutrophil Count (ANC), Low (cells/L)	0.800-1.000 x 10^9	0.600-0.799 x 10^9	0.400-0.599 x 10^9	< 0.400 x 10^9
Platelets, Decreased (cells/L)	100-125 x 10^9	50-100 x 10^9	25- 50 x 10^9	< 25 x 10^9
ALT or SGPT, High Report only one	1.25-2.5 ULN	2.5-5.0x ULN	5.0 - 10.0 x ULN	≥ 10.0 x ULN
AST or SGOT, High Report only one	1.25-2.5 x ULN	2.5 - 5.0 x ULN	5.0 -10.0 x ULN	≥ 10.0 x ULN
Creatinine, High	1.1-1.3 x ULN	> 1.3 -1.8 x ULN OR Increase to 1.3 - 1.5 x participant's baseline	> 1.8 - 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Potassium, Low (mEq/L; mmol/L)	3.0 -3.4 3.0 -3.4	2.5 - 3.0 2.5- 3.0	2.0- 2.5 2.0 -2.5	< 2.0 < 2.0

Normal range of laboratory (hematological and biochemical) parameters in SHW, SHM and SHT

Hematological and biochemical parameters	Normal Range
HGB (g/dL)	11-16
NEUT (10^3/μL)	2-7.5
PLT (10^3/μL)	150-400
ALT (U/L)	10-60
AST (U/L)	10-50
Serum creatinine (μmol/L)	53.0-114.9
Potassium (mmol/L)	3.5-5.5

Annex 4. Gantt chart

Activities	2019			2020			2021											
	November	December	January	October	November	December	January	February	March	April	May	June	July	August	September	October	November	December
Protocol	*	*	*															
Preparation				*														
Main study				*	*	*	*	*	*	*	*	*	*	*	*			
Data analysis															*	*		
Thesis writing															*	*	*	
Thesis defense																	*	*

Annex 5. Budget estimation

Item	Description	Estimation (Kyats)
1.	Stationary (e.g. printing, copy, etc.)	400,000
2.	Laboratory investigation fees	2,000,000
3.	Thesis book	300,000
4.	Miscellaneous	300,000
	Total	3,000,000

Rector - 692470
Registrar - 9699877
Assistant Registrar- 9690485
Fax - 9690486

The Republic of Union of Myanmar
Ministry of Health and Sports
Department of Human Resources for Health
University of Pharmacy, Yangon

3/278, Waibargi, (8)Qr, North-Okkalapa Township, Yangon

Letter No. 12/2020
Dated: 29-7-2020

The Ethics Review Committee on Medical Research Involving Human Subjects, University of Pharmacy, Yangon, approves to conduct the following proposed research project.

Research Title

Clinical Effectiveness and Safety of Amphotericin B with Flucytosine-Fluconazole Therapy for Cryptococcal Meningitis in Patients with HIV infection

Investigator: Zin Win May

Professor May Hla Thwin
Chairperson
Ethical Review Committee
University of Pharmacy, Yangon

(This approval is valid for the period of one year from the date mentioned.)