Improving Cryptococcal Meningitis Outcomes: A Mixed-Methods Evaluation of a Cryptococcal Meningitis Program and Barriers to Care in Rural Uganda

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ABSTRACT

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Cryptococcal meningitis (CM) is an important cause of death globally for those with HIV, as it is responsible for 15% of all AIDS deaths. With an estimated mortality rate of 50-70%, this disease continues to kill 181,000 people globally per year. Although there are established treatment guidelines for this disease to decrease mortality, the current Uganda guidelines for CM care are difficult to implement because hospital supplies are often out of stock and treatment is too expensive for patients, especially in rural areas. Additionally, little is known about the barriers related to care-seeking, diagnosis, and treatment to improve CM mortality and morbidity outcomes from the patient and provider perspectives. The purpose of this dissertation is to evaluate whether an ongoing CM Diagnosis and Treatment Program (CM-DTP) in Lira, Uganda improved care and outcomes for CM and to understand the patient, family member, and provider perspectives of the experiences they had with this disease. In conducting this evaluation, this dissertation also seeks to identify barriers and facilitators to care in order to improve CM diagnosis and decrease mortality outcomes in rural Uganda.

This dissertation is composed of five chapters, of which three focus on specific aims and assess different participant groups and components of the CM-DTP evaluation. The first manuscript is a retrospective chart review of all patients diagnosed with CM or meningitis or who had symptoms of meningitis seen between February 2015–February 2019 (N≈700). Two cohorts were set up in order to assess the effectiveness of the CM-DTP compared to a historical cohort in improving CM diagnosis and mortality outcomes (Aim 1a) and identify improvements in CM care (Aim 1b). The first cohort included patients seen from February 2015-2017 who received the usual care, referring to care prior to the implementation of CM-DTP. The second cohort included patients seen from February 2017-2019, who received care during the first two years of CM-DTP implementation. Utilizing the Intervention Mapping framework, we evaluated the CM-DTP and found that among patients who had a positive confirmed CM diagnosis, overall mortality trends decreased from cohort 1 to cohort 2 and that the number of antibiotics prescribed decreased while treatments with lumbar punctures (LPs), and combination Amphotericin B and fluconazole increased in cohort 2. Significant predictors of mortality were Glasgow coma scale of <15, while a decreased number of hospital days and an increased number of LPs were significantly associated with death. The purpose of this comparative study was to understand the effects of the program and thereby propose future interventions to improve CM care and decrease CM-related deaths in rural Uganda.

The second manuscript, Chapter 3, focuses on identifying barriers and facilitators to health-seeking behavior—from patients and family members perspectives—and to assess whether or not these participants were receiving accurate information from providers by gauging their knowledge of cryptococcal disease (Aim 2). For this mixed-methods study, survey and semi-structured interviews were conducted with patients (N=20) and family members of

deceased patients (N=20) who participated in the CM-DTP between February 2017-2019. Results from the surveys and themes from the interviews informed by the Integrated Behavioral Model (IBM) showed that the lack of CM education and understanding, stigma, and mental health disorders were key barriers, while support and purpose for life were key facilitators for CM care. Additionally, primary reasons for delays in CM diagnosis and care included self-medication, multiple visits to local health centers, and cultural/religious rituals which were used as alternative methods for treatment and healing. This novel information increases understanding of the barriers and facilitators patients encounter during the course of their CM experience within the program. The insights gained from this second manuscript will also inform future interventions to improve the current program and aid in early CM detection, treatment, and patient education about CM disease and prevention.

The third manuscript (Chapter 4) explores the experiences and perspectives of healthcare providers. An interview guide was developed using the IBM constructs to assess providers' knowledge surrounding CM care in order to a) identify barriers and facilitators in their ability to diagnose and treat CM and b) assess their knowledge of CM, cryptococcal screening, and treatment based on Uganda CM guidelines (Aim 3). Similar to the second manuscript, surveys and semi-structured interviews were conducted with providers (N=20) from outside health centers who referred patients to Lira Regional Referral Hospital (LRRH). The findings from the surveys and interviews identified the key barriers of lack of CM education and knowledge, lack of diagnostic and treatment supplies, and cultural/religious delays by patients, while facilitators included CM knowledge, educating patients on CM, and providing support for patients. The insights gained from this qualitative study helped identify key areas that will enable future interventions to equip providers with the needed knowledge, resources, and tools to ensure that patients receive appropriate CM care based on Uganda’s current guidelines regarding CM diagnosis and treatment. Understanding the barriers that providers have in diagnosing and treating HIV/AIDS patients with CM symptoms supplemented the findings gained from the qualitative study with patients and provided a more holistic picture of the gaps or inconsistencies that exist in CM-DTP and CM care in rural Uganda.

The overall purpose of this dissertation was to strengthen the CM-DTP and CM care in Uganda, which was accomplished by the identification of barriers and facilitators in care-seeking, diagnosis, treatment, and overall CM care through assessing patient and provider knowledge and experiences. Through the improvement of diagnosis, mortality outcomes, and overall CM care, we can enhance and preserve the lives of patients. The conclusion of this dissertation offers key recommendations to LRRH and Uganda Ministry of Health officials to improve CM patient education, services, and care.

Keywords*:* Cryptococcal meningitis, HIV/AIDS, program evaluation, mixed methods, Africa

DEDICATION

To the patients, family members, and providers who shared their time and personal stories. I hope by sharing your compelling experiences we can help more people know about cryptococcal meningitis so they can live a healthy and purpose-filled life. To the clinical and administrative staff at LRRH who contributed to this study, thank you for your insights and unending support for this project.

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LIST OF ABBREVIATIONS

AIDS	Acquired immune deficiency syndrome
Ampho B	Amphotericin B
ART	Anti-retroviral therapy
ARV	Anti-retroviral
CD4	Cluster of differentiation 4
CO	Clinical officer
CrAg	Cryptococcal antigen
CSF	Cerebral spinal fluid
CRF	Clinical record forms
CM	Cryptococcal meningitis
CM-DTP	Cryptococcal meningitis diagnosis and treatment program
CME	Continuing medical education
CEU	Continuing education units
GCS	Glasgow Coma Scale
GUREC	Gulu University Research Ethics Committee
HC	Health center
HIV	Human Immunodeficiency Virus
IBM	Integrated Behavioral Model
IM	Intervention Mapping
IRB	Institutional Review Board
IV	Intravenous
LFA	Lateral flow assay
LP	Lumbar puncture
LRA	Lord’s Resistance Army
LRRH	Lira Regional Referral Hospital
MO	Medical officer
MOH	Ministry of Health
OI	Opportunistic infection
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SSA	sub-Saharan Africa
TB	Tuberculosis
UNCST	Uganda National Council for Science and Technology
UW	University of Washington

CHAPTER 1: INTRODUCTION

Background

Cryptococcal meningitis (CM) is an infection of the central nervous system which presents with typical meningitis symptomology, such as headache, stiff neck, fever, and nausea.[6] It is most commonly caused by the yeast *Cryptococcus neoformans*, which is found in soil and bird droppings and transmitted to humans through inhalation.[7] For healthy people, this yeast is benign and does not cause ill effects; however, for those with compromised immune systems, such as those with HIV/AIDS, *C. neoformans* can cause CM, leading to severe morbidity such as blindness, deafness, paralysis, neurocognitive dysfunction, or death.[8] Deaths are likely related to lack of cryptococcal antigen screening, delayed presentation to care, delayed diagnosis and treatment, lack of availability of medication, lack of adherence to HIV medications, failure of HIV medications due to resistance, or a combination of factors.[3] With treatment, CM is curable; however, without appropriate treatment, this disease is fatal.[9]

Significance of Problem

Cryptococcal meningitis is one of the deadliest opportunistic infections (OIs) associated with HIV with a mortality rate estimated at 50-70%[9,10] and is responsible for 15% of all AIDS deaths. Despite widely available antiretroviral treatment (ART), CM continues to be an OI that kills 181,000 people globally per year, with most deaths occurring in sub-Saharan Africa (SSA).[11-20] The prevalence of CM varies between countries and ranges from 1.8-10.2%, with the highest burden affecting SSA.

Review of Literature

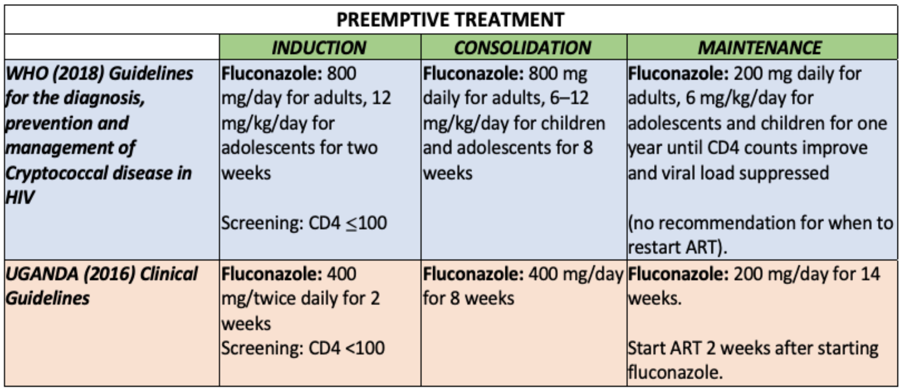
The purpose of the literature review was to identify and examine what is known about CM related to treatments (medications and procedures), education, training and qualitative perspectives from patients and providers who have experience with CM. From January to March 2019, searches were conducted for a scoping literature review. Manuscripts from 2008 to 2019 were included in the review, which used the PRISMA ScR checklist. Database searches included PubMed, Embase, CINHAL, and Google Scholar. The MeSH search terms included Cryptococcus, Cryptococcal, and Cryptococcal meningitis, with supporting terms of treatment, lumbar puncture, prevalence, delay, education, training, teaching, qualitative, interview. Additional articles were found from references from previous studies. Search results and additional articles (titles and abstracts) were reviewed for eligibility criteria of 1) co-infection with HIV, 2) studies conducted in SSA or resource-limited areas, 3) first-time occurrence with CM, and 4) sample population >50. A sample population criterion was included because some studies had a sample population of <50 with <10 patients who had confirmed CM, leading to insufficient significance of data findings. This criterion was applied to more robust study topics such as treatments, which had a higher number of results of higher quality studies. For qualitative studies, no sample size exclusions were applied, as case studies were included. The initial database review yielded 1,271 articles and 647 duplicate articles were removed. Titles and abstracts were further screened for relevance, which decreased results to 281 articles. A full-text review of these articles was conducted which narrowed our articles to 33 which were then used for the scoping review.

The findings of the literature search showed standard and recommended practices for CM treatment are sometimes difficult to implement, particularly in parts of SSA where some treatment regimens and supplies are unavailable outside of a randomized control trial or study setting. Barriers and gaps to CM care were discovered during the review process, which prompted further literature searches on the topics such as treatment delays and CM education for patients and providers. The findings, detailed below, were categorized by the types of treatments of preemptive and CM treatments and lumbar punctures, usual treatment and care for CM, and barriers and gaps in CM care.

Types of CM Treatment

Preemptive and CM Treatments

Table 1.1. WHO and Uganda CM Preemptive Treatment Guidelines



PREEMPTIVE TREATMENT			
	INDUCTION	***CONSOLIDATION***	***MAINTENANCE***
WHO (2018) Guidelines for the diagnosis, prevention and management of Cryptococcal disease in HIV	**Fluconazole:** 800 mg/day for adults, 12 mg/kg/day for adolescents for two weeks Screening: CD4 ≤100	**Fluconazole:** 800 mg daily for adults, 6–12 mg/kg/day for children and adolescents for 8 weeks	**Fluconazole:** 200 mg daily for adults, 6 mg/kg/day for adolescents and children for one year until CD4 counts improve and viral load suppressed (no recommendation for when to restart ART).
UGANDA (2016) Clinical Guidelines	**Fluconazole:** 400 mg/twice daily for 2 weeks Screening: CD4 <100	**Fluconazole:** 400 mg/day for 8 weeks	**Fluconazole:** 200 mg/day for 14 weeks. Start ART 2 weeks after starting fluconazole.

There are two treatment groups for cryptococcal disease or exposure: a) people who have a positive serum or whole blood CrAg titer and are asymptomatic but need preemptive outpatient treatment and b) cerebral spinal fluid (CSF) positive confirmed CM via CSF culture, India ink, or CrAg LFA who need intensive treatment and hospitalization. Recommendations for treatment have been made for both groups which involve the use of fluconazole in the inductive, consolidation, and maintenance phases of treatment for both inpatient and outpatient care[19,20,22,23] (Table 1.1). Each treatment group (preemptive or CM) incorporates each of these treatment phases. The inductive phase refers to the most aggressive period of treatment to decrease the disease fungal load as quickly as possible, while the consolidation and maintenance phase refers to the slow tapering of anti-fungal medication to continue the reduction and elimination of the fungus and to prevent disease recurrence. The inductive and consolidations phases are typically monitored during the hospitalization of the patient. The maintenance phase has the longest period of treatment, lasting weeks to years on an outpatient basis, depending on country guidelines and whether treatment is preemptive or for CM disease. Most guidelines recommend initiating or restarting ART medications two weeks after preemptive treatment[19,24] or restarting 4-6 weeks after CM treatment. The cryptococcal optimal ART timing (COAT) trial showed higher mortality in patients who were started on ART 1-2 weeks after CM diagnosis compared to those who started 5 weeks after diagnosis.[13] It was unclear whether the excess deaths were attributed to unmasking immune reconstitution inflammatory syndrome (IRIS) or due to the progression of CM.[12,25-27] Irrespective of the cause of death, overall outcomes were worse for those who had early ART initiation compared to deferred ART (Hazard ratio 1.73 CI: 1.06-2.8 p= 0.03) by 26 weeks.

Therapeutic Lumbar Puncture (LP)

An effective non-pharmacological treatment for the headache symptoms in CM is the LP. Headache is the most common complaint of CM, and this is due to the excessive intracranial pressure that builds up in the brain. This pressure is caused by the accumulation of fungal cells which block the arachnoid villi (finger-like projections in the cranial venous sinuses that reabsorb CSF), which in turn, creates excess fluid in the brain.[29] The excess fluid and pressure not only cause headaches, but neurocognitive deficits like vision and hearing loss, loss of consciousness and death.[13] To relieve this pressure, external extraction of CSF can be accomplished through therapeutic LPs. This requires a spinal needle to be inserted into the subarachnoid space, allowing CSF to be removed manually.[26] Some side effects of LPs are post-procedural headache, back pain, bleeding, and infection. Pain medications are given for pain, and antibiotics are prescribed for infection as needed. Patients should lay on their back after the LP is finished to prevent bleeding and minimize headaches.[26] The amount of CSF taken during an LP is based on the opening pressure, which is measured by a manometer.[19] However, in many settings in SSA, a manometer is unavailable.[19] One study found that those who did not have opening pressures measured had less CSF removed, in addition to having fewer therapeutic LPs during hospitalization.[31] The addition of therapeutic LPs to the patient's treatment plan has been shown to improve mortality outcomes in addition to increasing comfort.[26] Current guidelines for therapeutic LPs are in place depending on national and country recommendations. Some guidelines suggest daily therapeutic LPs, whereas others predicate LPs on CSF pressure. The WHO advises to continue daily LPs if opening pressures are >20 cm H_2O with drainage of 20-25 ml of CSF.[22] Once symptoms resolve and pressures are <20 cm H_2O for 2 days or longer, LPs can conclude.[17] Studies showed improved mortality when patients received routine therapeutic LPs during the course of induction therapy. One study from Tanzania showed mortality improvement from 75% to 46%.[32] while a study in Uganda and South Africa showed a reduction in mortality risk by 69% by implementing routine therapeutic LPs.[32]

There is no consensus regarding the quantity of therapeutic LPs that need to be performed during the induction phase of CM treatment, but there is consensus that therapeutic LPs are effective in reducing symptoms for patients and are associated with improved mortality. Malawi is currently one of the few countries that recommends daily LPs in their clinical management guidelines.[32]

There is a history of resistance to LPs from patients, as evidenced by a screening study where 17 out of 28 patients who had a CrAg positive screen refused an LP to rule out CM.[32] One reason for refusal is the belief that LPs will cause death; people associated LP procedures with the high mortality outcomes of CM.[13] This belief reflects the limited education given to patients regarding this treatment.[20] In rural areas where providers have limited experience performing this procedure, they may be more reluctant to pursue or recommend this treatment.

Results from an informal survey found that some providers deferred LPs due to the fear of brain herniation.[33] Time is also a factor in deferring this procedure, especially if there is only one provider on duty.[34] For inexperienced providers, this procedure may take multiple attempts, especially when there are spinal abnormalities or with uncooperative patients. Lastly, the availability of spinal needles and manometers is lacking in rural areas.[33] These issues present barriers. To improve LP uptake, education is needed for both providers and patients, as well as hands-on training and practice for providers. LP supplies also need to be available so that the tools are in place and providers can easily perform the procedure.

Usual Treatment and Care for CM

Standard treatment for CM in Uganda includes Ampho B, which involves IV infusions with normal saline before each Ampho B dose, routine therapeutic lumbar punctures (LPs), and bi-weekly blood specimen testing. Without proper and frequent monitoring and supplemental medications, patients can die from nephrotoxicity, anemia, and electrolyte imbalances from the medication.[34] A study in Botswana examined Ampho B use and found high mortality rates during routine usual care conditions, with 53% of patients missing at least one dose of Ampho B during their treatment course, which was highly associated with higher mortality over each follow-up period (2 & 10 weeks, 1 year).[35] Some of these missed doses were potentially due to serious side effects prompting the discontinuation of treatment until side effects improved or from the challenges of administering a high maintenance medication like Ampho B.[5,14,15] The study also found that monitoring of electrolyte levels was performed infrequently and that less than half of the sample had therapeutic LP procedures. Certain treatments were not available for all patients, which may have contributed to increased mortality. The study also assessed usual care, which was care that was given with current available resources at the study site, with no additional services or supplies provided. No studies, outside of a treatment studies, were found that assessed or evaluated a CM program which provided supplemental supplies and staffing for CM treatment conducted in a rural setting of a sub-Saharan African (SSA) country.

Barriers and Gaps in CM Care

Delays

Several studies suggested that one reason for high mortality among CM patients was delay of care. Two types of delay were identified: one related to ART initiation and the other related to CM care and treatment. Both types of delays are associated with each other, as CM is attributed to immunodeficiency evidenced by low CD4 counts. This cascade of immunodeficiency is associated with poor outcomes and death among patients with CM. Despite the widespread availability of ART, public education about HIV, and encouragement for HIV testing and treatment, a delay in ART initiation still exists. Many studies sought to understand the barriers and facilitators of HIV testing and treatment and indicated stigma as a major barrier. Other studies found that CM treatment delay was potentially due to limited resources for medication, lack of diagnostic testing kits, and limited staff training for complex medical management.[5,11,33]

Suggestions to improve delays associated with CM care and treatment included focusing on logistical factors such as providing adequate supplies for CM treatment and diagnostics and early detection through screening. However, these interventions do not address or answer the reasons why patients present "late" for CM care, when treatment is less successful and outcomes become dire. A gap in research was identified related to the patient's care-seeking behavior for CM care and treatment based on their experience. It is unknown whether they have purposefully delayed care or whether there was a delay in CM care due to misdiagnosis or another undocumented factor. This is an area of CM research that needs to be investigated, as studies have shown that earlier diagnosis of CM would reduce CM related deaths. Understanding barriers and facilitators to CM care from the patient and provider perspectives will provide information on what interventions need to be put into place to address these delays, improve CM outcomes, and mitigate long-term disabilities.

CM Education

Education regarding CM guidelines for screening, diagnosis, and treatment has been ongoing for health professionals, and studies recommended continued education to improve CM outcomes.[37] Education of health professionals keeps them abreast of changing national guidelines for the screening, diagnosis, and treatment of CM and is crucial for proper care and improvement of mortality outcomes. Some efforts have been made towards health worker education, and studies have recommended patient and public education related to HIV disease and treatment; however, it is unknown how much education is provided because there is little documented evidence of cryptococcal disease education to HIV patients.

A case study in Gulu, Uganda chronicled one patient's journey of CM diagnosis and showed that the patient was re-diagnosed with CM 3 months later due to lack of follow-up and failure to complete treatment.[15] The authors stated, "(the patient) was not aware of the cause, treatment options, and duration and the need for long-term/life-long suppression therapy for (their) condition."[44] This is a failure on the part of the health providers, who did not provide this patient with adequate information and education regarding their condition and illness during their initial hospitalization. Although this is one patient's story, this may be a common occurrence. Recommendations from this study emphasized that cryptococcal disease awareness not be limited to health professionals but include education of patients and stakeholders regarding the severity of the illness and importance of long-term suppressive anti-fungal therapy.[19,20] This is one of the only studies identified which provided a patient's medical history with CM.

Comprehending the pervasiveness of these knowledge and education gaps at the patient and provider levels can inform the development of appropriate interventions to address them. Awareness of screening, the disease, and its symptoms can improve CM outcomes when knowledge and recognition of symptoms motivates patients to actively seek care sooner and healthcare providers deliver timely and accurate diagnoses.

In summary, findings from the literature review revealed current standards for CM care and identified gaps in patient and provider education on CM and its treatment, delays in treatment due to unavailability of necessary supplies for diagnosis and treatment, patient-related delays, and unknown outcomes of providing standard of care in rural settings of Uganda.

Background of CM and CM Treatment in Uganda

In Uganda, CM is the second most common cause of HIV-related death behind tuberculosis (TB), with a mortality rate ranging from 20-42%.[33] In 2016, the Ugandan government implemented updated guidelines for screening, testing, and treating CM in HIV-infected persons.[19,45] The guidelines for the induction phase of CM treatment include: CrAg testing; combination therapy with antifungals such as fluconazole, intravenous (IV) Amphotericin B (Ampho B), or flucytosine; IV hydration; therapeutic lumbar punctures (LPs); routine blood testing; and supplemental electrolytes. To implement these guidelines, the government should ideally provide hospitals with CrAg testing kits and antifungal medications for treatment; however, in practice, supplies are often out of stock and treatment is too expensive for patients to buy, leading to inadequate treatment and subsequent mortality and morbidity. CM treatment, which incorporates combination therapy using Ampho B and fluconazole, can improve outcomes,[46] but challenges of intensive time and labor are associated with Ampho B administration, which is given daily for 7-14 days.[48] (Table 1.2) Therapeutic LPs and routine monitoring of electrolyte levels, kidney function, and blood counts should be performed routinely for optimal outcomes.[48]

Table 1.2. Uganda CM Treatment Guidelines

CM TREATMENT			
	INDUCTION	***CONSOLIDATION***	***MAINTENANCE***
UGANDA (2016) Clinical Guidelines	**Amphotericin** B: 0.7-1 mg/kg/day + **Flucytosine:** 100 mg/kg/day (in four divided doses) for 2 weeks **ALTERNATIVE** **Amphotericin** B: 0.7-1 mg/kg/day + **fluconazole:** 800 mg/day (12 mg/kg in children) for 2 weeks **ALTERNATIVE** **Amphotericin B:** 0.7-1 mg/kg/day + **fluconazole:** 800 mg/day, (12 mg/kg in children) for 5-7 days **ALTERNATIVE** **Fluconazole:** 1200 mg/day (12 mg/kg/day in children and adolescents <19 kg)	**Fluconazole** 400-800 mg/day (or 6-12 mg/ kg/day in children) for 8 weeks if Amphotericin is used in induction phase **OR** **Fluconazole** 800 mg (12 mg/kg/day) for 8 weeks if amphotericin short course-high dose fluconazole regimen used *Commence ART 4-6 weeks after starting CM treatment and if there is clinical response to antifungal therapy*	**Fluconazole** 200 mg/day (or 6 mg/kg/day max 200 mg for children) **DISCONTINUING:** Stopping after 1 year of maintenance phase: Adults VL <1,000 copies/mm3 & CD4 ≥100 for 6 months or CD4 ≥200 if viral load not available.

Setting

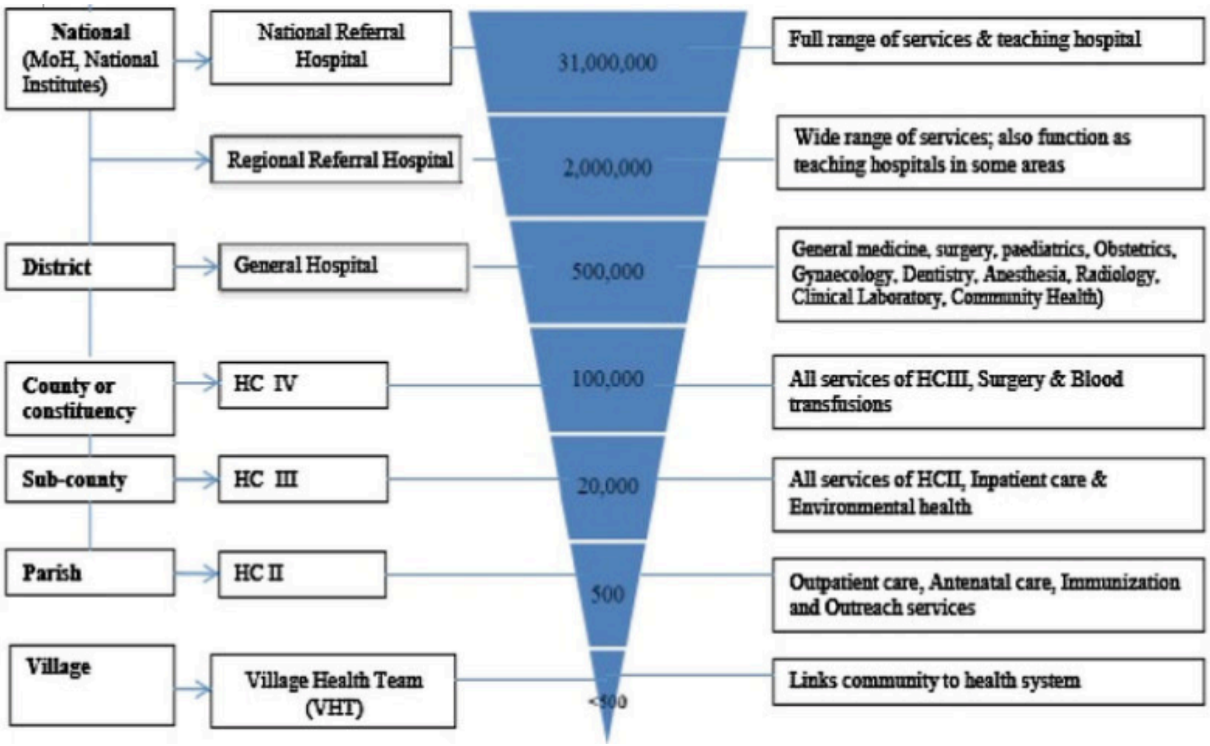
Lira Regional Referral Hospital (LRRH) is a rural government referral hospital located in northern Uganda and is one of 117 referral hospitals in the country.[4] This northern area of Uganda was under rebel occupation led by Joseph Kony and his Lord's Resistance Army (LRA) from 1987 to 2006.[4] During the years of civil war, this area was neglected and had

Figure 1.1. Map of Uganda[1]

poor access to healthcare and other resources. Over the past 14 years, there has been much improvement: increased infrastructure, improved health facilities, and population growth. LRRH currently serves nine surrounding districts with a catchment area of 2.2 million people.[4] The hospital has several specialty services including surgery, maternity, gynecology, neonatal intensive care, palliative care, ophthalmology, and psychiatry, with 1300 admissions each month.[11]

Nine districts surround the hospital, and several district hospitals and clinics—health center (HC) II, III, IV, and private facilities—refer patients. The lower-level heath facilities (HC II and III) are the first line of care for medical evaluation for patients and determine how quickly a patient is diagnosed and treated for diseases. The structure of the Ugandan healthcare system looks like an inverted triangle: the lower-level health care cadres serve the local population, while higher-level HCs serve the larger community, including referrals received from the lower-

Figure 1.2. Uganda Government Health Care Structure[4]



level HCs (Figure 1.2). There is also a referral system which typically moves patients from one HC level to the next until the patient is finally referred up to the HC that can provide the care the patient needs. Additionally, if patients are initially cared for at a private facility, they are commonly referred to a government or regional referral hospital if they encounter financial constraints.

A typical HC II provides outpatient preventive and promotive services for approximately 500 community residents, while HC IIIs provide maternity and some inpatient services, as well as basic laboratory services for a population of 20,000 people.[17] HC IVs have more traditional responsibilities of a general hospital and can provide outpatient, inpatient, maternity care, emergency surgery, blood transfusions, and laboratory services, whereas referral hospitals like LRRH can provide everything that a HC IV can with the addition of specialized care like psychiatry, radiology, ophthalmology, and surgical services.[5,7,33,37,42] The national hospital is the highest level of care and is where referral hospitals send patients when they are unable to care for the higher medical demands of the patient. Nurses and allied health professionals make up the majority of the healthcare staff in the lower-level facilities, especially in rural areas, while medical officers are more commonly found in the urban areas, where they work at HC IV sites.

Background of the Cryptococcal Meningitis Diagnosis and Treatment Program

In 2017, an assessment of usual care for CM patients at LRRH observed that supplies needed for CM treatment (e.g., Ampho B, fluconazole, electrolyte supplements, lab monitoring, CrAg LFA testing kits) were often lacking or unaffordable for patients, leading to sub-optimal treatment and increased deaths. The findings from this assessment initiated a CM program through a collaboration between LRRH, the Infectious Diseases Institute of Makerere University, and the University of Minnesota to support the implementation of a CM Diagnosis and Treatment Program (CM-DTP) based on Uganda's CM clinical guidelines (Table 1.2). This program, which began in 2017, provided supplemental supplies for diagnosis, treatment, patient monitoring, dedicated staff, and outpatient follow-up.

Problem Statement

CM care in rural areas of Uganda faces unique challenges compared to urban areas. These challenges include, but are not limited to, medication shortages, diagnostics, laboratory reagents, and lack of training and education for healthcare providers and patients. Many of these gaps and barriers were observed during the baseline assessment prior to the CM-DTP and led to high mortality rates in CM patients at LRRH. CM is a treatable disease, and with proper and timely treatment, lives can be saved. The findings from the baseline assessment prompted the initiation of this program.

Providing CM-DTP should improve outcomes; however; if patients present too late during their illness or if their diagnosis or treatment is delayed, CM treatment may not help. Many studies attributed delays related to diagnosis, treatment, and patient presentation to healthcare facilities with poor outcomes for CM patients; however, little is known about why these delays exist or how to counter them.

Ascertaining the pervasiveness of knowledge and education gaps at the patient and provider levels can provide justification for the development and implementation of education programs at health facilities and the community. Although researchers recommended patient and public education related to HIV disease and treatment, there is minimal evidence from the literature that this education includes information on cryptococcal disease or OIs. Awareness of the disease and its symptoms can improve CM outcomes if a) knowledge and recognition of symptoms and other factors of behavior motivate patients to actively seek care sooner and b) healthcare providers deliver timely and accurate diagnosis and treatment. Additionally, understanding the barriers and facilitators to CM care from the patients' and providers' perspective helped to identify gaps surrounding current CM care to inform future interventions that will improve patient outcomes.

Purpose

In response to high mortality rates and inadequate supplies to treat CM at LRRH, a standard of care program (CM-DTP) was started in 2017. The purpose of this research was to evaluate whether the CM-DTP (February 2017-February 2019) improved CM care and improved mortality outcomes for CM compared to usual care from an historical cohort (February 2015-February 2017). In addition, this study aimed to identify barriers and facilitators to CM care, knowledge, education, diagnosis, treatment, and behaviors which can inform future interventions to decrease rates of CM mortality and morbidity in rural Uganda.

Rationale

To improve CM mortality outcomes, we need to assess whether the CM-DTP was effective in reducing mortality and to understand the patient and healthcare provider experiences related to overall delays, CM education, and other barriers and facilitators to CM care. Obtaining this information will help inform LRRH staff, administration, and other healthcare facilities on which future intervention strategies and guidelines should be prioritized to improve the CM-DTP and the overall care for CM patients in rural areas of Uganda.

Specific Aims

We hypothesized that patients who participated in the CM-DTP experienced improved diagnosis and treatment of CM, leading to decreased mortality outcomes at LRRH compared to patients who received usual care. Additionally, understanding the experiences of patients and healthcare providers surrounding CM care-seeking, diagnosis, and treatment can identify gaps in care.

Aim 1a: Determine whether patients who received care through the CM-DTP had improved CM diagnosis and decreased mortality outcomes compared to patients who received usual care.

Aim 1b: Identify improvements in CM care which occurred during the implementation of the CM-DTP.

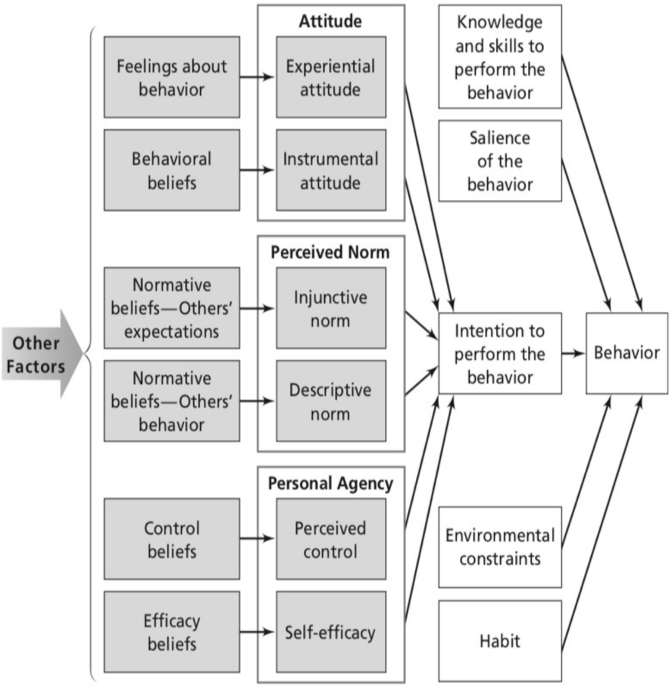
Aim 2: Understand the patient's CM experiences who were a part of the CM-DTP and identify barriers and facilitators to health-seeking behavior, diagnosis, and treatment and assess their knowledge regarding cryptococcal disease.

Aim 3: Elucidate the provider's behaviors, to identify barriers and facilitators to their ability to diagnose and treat CM, and to assess their knowledge of CM, cryptococcal screening, and treatment based on Uganda CM guidelines.

Theoretical Model

The Integrated Behavioral Model (IBM) was used to develop the surveys and qualitative interviews and is the theoretical model identified in step 3 of the Intervention Mapping Evaluation framework. The IBM is an extension of the Theory of Reasoned Action and the Theory of Planned Behavior, and asserts that the best predictor of performing a behavior is its linked intention or motivation.[51] It is a behavioral model that incorporates additional factors which may affect behavioral intention such as the environment, habit, knowledge, salience of the behavior, while incorporating three key theoretical constructs of attitude, perceived norms and personal agency[49] (Figure 1.3). In the qualitative interviews, we identified each key construct and factors related to the behavior of going to a clinic for medical care. The interviews provided further understanding of key theoretical constructs that may affect care-seeking behavior.

Figure 1.3. Integrated Behavioral Model (IBM)



In IBM, the construct of attitude is categorized as experiential and instrumental. Experiential attitude or affect is the emotional response to performing a behavior, which could be assessed by how someone feels about going to a health clinic for care. Instrumental attitude (cognitive) is based on one's beliefs of the positive and negative outcomes of engaging in a behavior[52] and could be expressed by someone's belief that going to the clinic will or will not improve their health. The construct of perceived norms is defined as the external pressures placed on a person to perform a behavior. There are two types of norms. Injunctive norms are beliefs or expectations that one holds for themselves based on whether others will support their behavior, and descriptive norms are the perceptions or beliefs of how other people who are within their social circle (social or cultural norms) are behaving in relation to the defined behavior.[53] These two norms could be evidenced by one's concern or perception of whether the people around them would support their action or behavior (injunctive norm) and whether people in their own social group or family have the same action or behavior (descriptive norm). The theoretical construct of personal agency consists of perceived control and self-efficacy. Perceived control is based on the idea by Icek

Ajzen, that behavioral performance is motivated by intention and ability[52] and is defined as the amount of control over one's behavior and how easy or difficult it is to perform a behavior. Self-efficacy describes one's confidence or ability to perform a behavior. This can be assessed by someone's response to how confident they feel to physically go to the clinic.

In addition to these three constructs, IBM suggests that there are other factors that are needed besides intention, in order for an individual to perform a behavior in spite of difficulties or barriers. The IBM also a) incorporates knowledge and skills to perform the behavior; b) assumes that there are no environmental constraints to the behavior, such as physical or financial constraints to go to the clinic; c) assumes that the behavior is salient; and d) is facilitated by habit or the repeated behavior of going to the clinic regularly.[54] This model provides a more comprehensive understanding of behavior than other traditional behavioral models, as the IBM incorporates other factors such as the environment and knowledge which may also affect behavior.

This dissertation utilized the constructs from this model to formulate questions for the surveys and semi-structured interviews and guided identification of the determinants in the IBM. Incorporating this model in the studies provided greater understanding of the gaps and drivers for care-seeking, treatment, and care behaviors in patients and for diagnosis, testing, and treatment in providers.

Evaluation Framework

The Intervention Mapping (IM) framework was used for chapter two (Aim 1) of this dissertation to evaluate the program goals of increasing CM diagnosis and decreasing mortality. The IM was developed by Bartholomew, Kok, and Parcel in 1998 to provide a framework for health education programs and guide the process of developing health behavior interventions.

This framework was developed in response to gaps found between behavior and social change theories in health education intervention programs.[52,55] It applies social and behavior science theories for planning, implementing, and evaluating health programs. The six steps of this framework are to 1) perform a needs assessment, identify the program goals and develop a logic model of the problem; 2) state performance objectives for behavioral and environmental outcomes from the intervention and develop a logic model for change; 3) select a theoretical method (defined through theory and research) and practical strategies to apply the method; 4) refine and organize program structure, pretest, and refine intervention materials; 5) develop a plan for program implementation, promote program adoption, and design implementation interventions; and 6) specify the evaluation design and evaluate the effects of the program based on the program aims (Figure 1.4). These steps are iterative, and as more knowledge is gained, it can inform previous steps and provide new perspectives of current steps. Steps can be revisited and repeated if further information is

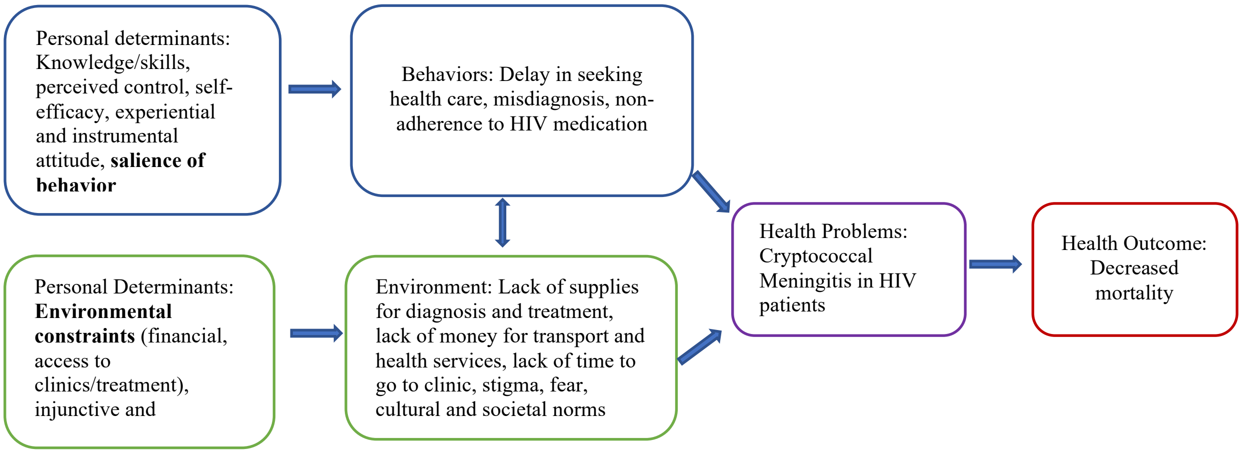
Figure 1.4. Intervention Mapping Framework

STEP	TASKS
Step 1 **Logic Model of the Problem**	• Establish and work with a planning group • Conduct a needs assessment to create a logic model of the problem • Describe the context for the intervention including the population, setting, and community • State program goals
Step 2 **Program Outcomes and Objectives – Logic Model of Change**	• State expected outcomes for behavior and environment • Specify performance objectives for behavioral and environmental outcomes • Select determinants for behavioral and environmental outcomes • Construct matrices of change objectives • Create a logic model of change
Step 3 **Program Design**	• Generate program themes, components, scope, and sequence • Choose theory- and evidence-based change methods • Select or design practical applications to deliver change methods
Step 4 **Program Production**	• Refine program structure and organization • Prepare plans for program materials • Draft messages, materials, and protocols • Pretest, refine, and produce materials
Step 5 **Program Implementation Plan**	• Identify potential program users (implementers, adopters, and maintainers) • State outcomes and performance objectives for program use • Construct matrices of change objectives for program use • Design implementation interventions
Step 6 **Evaluation Plan**	• Write effect and process evaluation questions • Develop indicators and measures for assessment • Specify the evaluation design • Complete the evaluation plan

obtained and should be continually re-evaluated throughout the course of the program [56]. For this evaluation, specific parts of steps 2, 3, 5, and 6 were utilized from this framework, as steps 1 and 4 were previously conducted.

Step 1 (the needs assessment) was done prior to the start of the CM-DTP and was informed by the literature, historical trends/gaps in CM care, preliminary data from LRRH patients seen and treated for CM and meningitis, and observations and personal accounts from staff at LRRH. This assessment found high rates of mortality and morbidity in CM among HIV patients at LRRH. After the health problem(s) were identified, the quality of life outcomes or the impacts of the health outcomes were stated (increased CM diagnosis and decreased mortality). This step also incorporates the identification of the behaviors and environmental factors related to the health problem (making it better or worse), as well as the behavioral and environmental factors that contributed to the health problem. The logic model in Figure 1.5 was based on the information identified from the needs assessment with the incorporation of the IBM constructs of behavioral intention and the factors which affect behavior. This information and the model of the problem was used to inform step 2 of the IM framework.

Figure 1.5. Logic Model of the Problem



Step 2 (Program Outcomes and Objectives) identified what changes were expected due to the intervention of CM-DTP. The CM-DTP indicated that CM diagnosis and mortality would improve as the result of the interventions. The change objective depicts the relationship between the theory and evidence-based change methods. An example objective in figure 1.6 incorporated the personal determinants identified from step 1, and performance objectives or specific behaviors and/or environmental factors performed by the target population (patients and providers) in order to enact change.[1] The change objectives were answered through the findings of the data analysis, and projected objectives were outlined in the logic model of change (Figure 1.7). The findings from the analysis of the surveys and interviews informed the outcomes of the performance objectives.

Figure 1.6. Change Objective

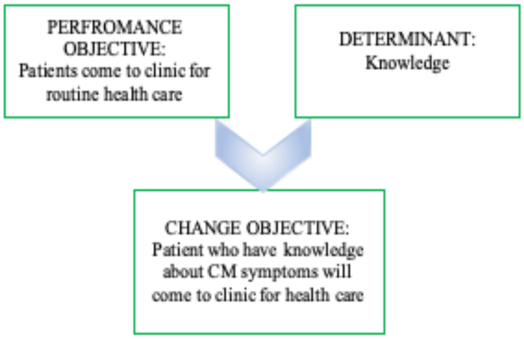
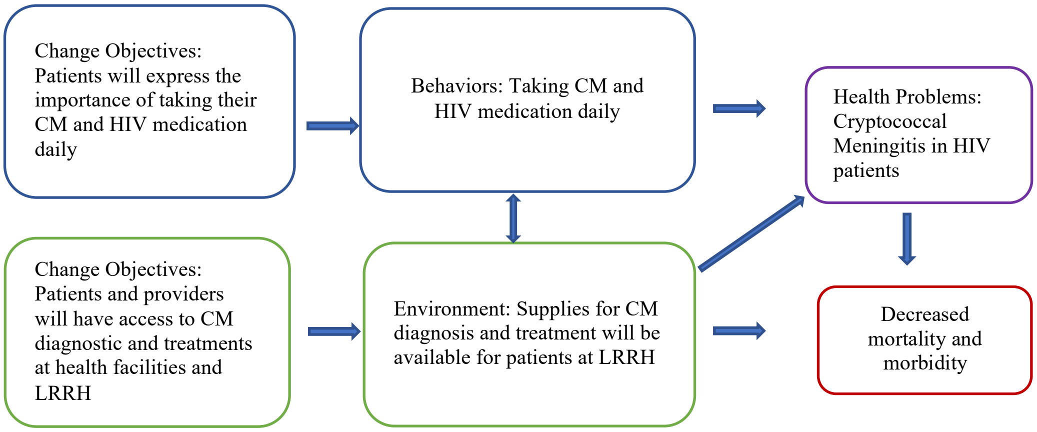


Figure 1.7. Logic Model of Change



Step 3 (Program Design) generated the program's scope, sequence, identified the change theory, and translated the theory-based methods into strategies based on the determinants to fulfill the change objectives. The scope of the program provided supplemental supplies,

treatment, and staff support for CM patients at LRRH to provide CM care based on Uganda's guidelines in order to improve diagnosis, care, and mortality. The program's design was a quasi-experimental design, which compared cohort 1 (usual care) to cohort 2 (CM-DTP) to estimate the effect of the program for the proposed outcomes. The program provided hands-on guidance and support to LRRH medical staff to deliver a standard of care based on Ugandan guidelines, ensuring that all patients with CM at LRRH were provided the appropriate medications and care to treat this deadly disease. LRRH staff were introduced to the Infectious Diseases Institute (IDI) staff who developed evidence-based CM practice protocols for patients at their clinic in Kampala, based on Ugandan and WHO guidelines. The IDI staff shared their experiences and provided the protocols which were used in the CM-DTP. These protocols included: initial CSF and/or blood testing with CrAg LFA test kit for CM; CSF and blood cultures; daily Ampho B infusions for 7-10 days; 1 liter pre-load and after-load with normal saline with each Ampho B dose; daily oral fluconazole, magnesium, potassium and calcium; therapeutic lumbar punctures (LPs) when patients complained of headaches, intercranial pressure measurement with a manometer; bi-weekly electrolyte and hemoglobin levels; and daily assessment by medical doctor or nurse. Although most treatments and procedures were not new to LRRH staff, the frequency, timing, and rationale for treatment and availability of supplies to provide this level of care were unclear or missing components prior to the start of the CM-DTP. The theory chosen for this evaluation was the IBM, which guided the identification of the environmental and behavioral determinants of behavior and informed the analysis of the intentions and behaviors related to attitudes, perceived norms, personal agency, knowledge, environmental constraints, salience of behavior, and habit.

Step 4 (Program Production) included refining the program, drafting the protocol and improving program materials. The CM-DTP protocol was based on a current CM protocol from the IDI, following the Uganda Clinical Guidelines. This protocol involved testing all suspected meningitis patients using CrAg lateral flow assay (LFA) testing kits, daily Ampho B infusions for 10-14 days with daily oral fluconazole, electrolyte supplements, daily assessment by program staff, routine lab monitoring and routine therapeutic LPs, and intercranial pressure measurements for symptoms. Supplies that were unavailable at the hospital were procured from a private pharmacy in Lira with an account which was set up for the program. Additionally, supplemental laboratory testing was performed at a nearby clinic, and payment arrangements were made between the program and the clinic. Representatives of the primary healthcare providers, supervisors, and the medical director of LRRH were presented with the CM-DTP to obtain their feedback and questions. On review of the IDI protocol, there were some items that were not available at LRRH, such as the manometers. The protocol was tailored to not measure intercranial pressure, but to draw off a standard 20-30 milliliters of CSF based on the flow of the fluid and the headache severity at each therapeutic LP. Additionally, CRF forms were reviewed, and questions that did not pertain to the program and procedural results due to the inability of being obtained at LRRH (CSF or blood cultures, CT scans) were omitted.

Step 5 (Program Implementation) identified the program users, outcomes and performance objects for the program, and designs for the implementation interventions. The program provided supplemental supplies, testing, treatment and staff in order to deliver standard of care interventions and implement program protocols for patients to decrease CM mortality and morbidity outcomes. The users of this program were the LRRH medical staff, study staff, and the patients. Prior to the start of the program, study staff were required to complete an online good clinical practice training through the CITI program website. This certified study staff on responsibilities and expectations for conducting, monitoring, reporting and documenting of clinical trials and bioethics. This program had multiple interventions provided by the medical staff for the CM patients at LRRH. The comprehensive list of interventions is included in table 1.3. The program also provided supplemental medications and supplies and provided additional supplies which the hospital did not carry (Table 1.4).

Table 1.3. CM Diagnosis Treatment Program (CM-DTP) Interventions

1.	Testing all patients who had suspected meningitis or CM via CrAg LFA blood and/or CSF at the time of initial assessment through the emergency room or the hospital ward
2.	Screening CRF forms initiated
3.	Enrollment of all CM positive patients for the CM-DTP
4.	Initiation of first Ampho B treatment, fluconazole, supplemental minerals, electrolytes and baseline lab work
5.	Interviewing patient/family members of illness history and other CRF related documentation
6.	Daily medication, assessment and supplemental pain or nausea medication
7.	Routine therapeutic LPs (based on patients' headache, pain or other symptoms), bi-weekly hemoglobin/electrolyte levels
8.	Outpatient follow-up with study staff at 2, 4, 8, 12, 24, 36 weeks, 1 year, 1.5 years and 2 years with maintenance fluconazole provided until CD4 >100

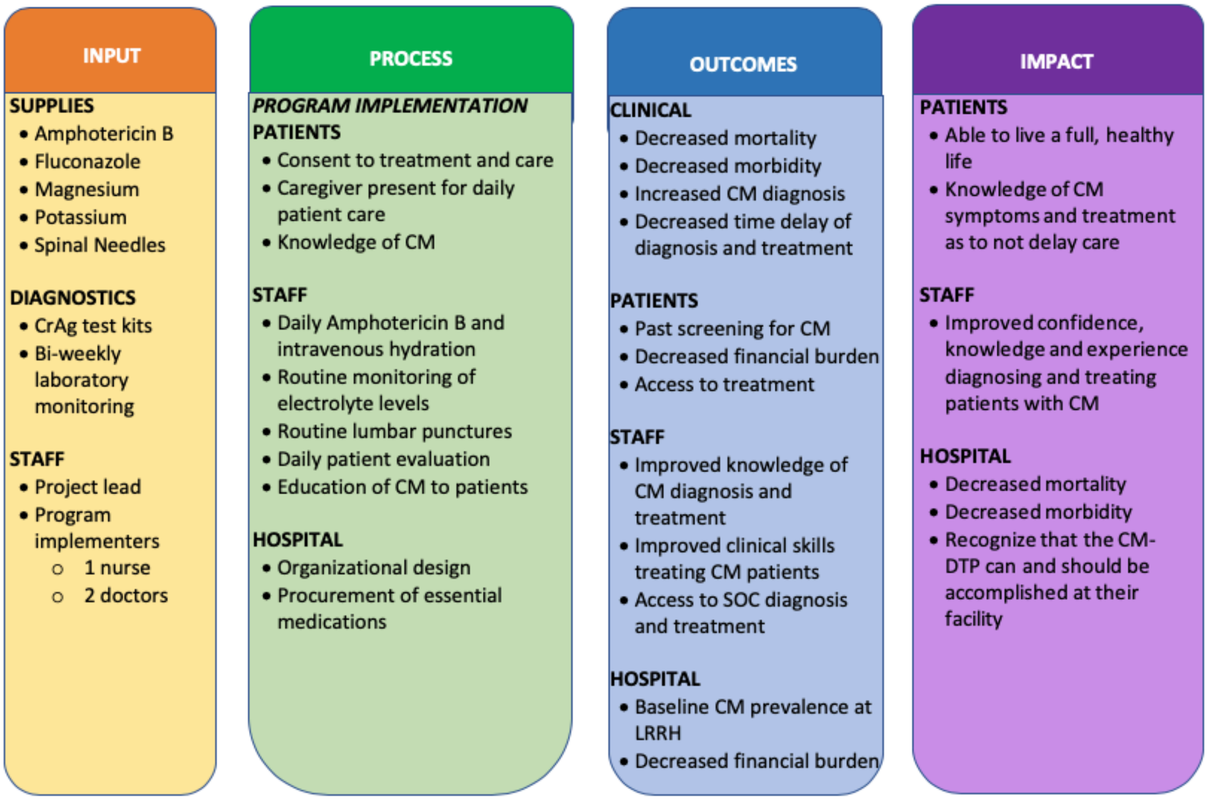
Table 1.4. CM-DTP Procurement

1.	Medications: Zofran, supplemental Ampho B, magnesium, potassium, fluconazole, normal saline
2.	Supplies: Sterile gloves, spinal needles, alcohol wipes, CrAg test kits, IV needles, IV tubing
3.	Laboratory: Supplemental, outside lab testing for hemoglobin and electrolyte levels
5.	Study staff salary: Site supervisor, two doctors, one nurse, data management
6.	Equipment: Computer, locked file, locked cabinet, internet, printer, printer cartridges, paper, refrigerator
7.	Miscellaneous: Patient transport fees for follow-up appointments

Step 6 (program evaluation) determined the effects the program had on specific outcome measures related to behavior, environment, and health.[2] Specific questions also addressed the understanding of how and why the outcomes were achieved. A logic model framework guided the evaluation (Figure 1.8). Inputs were identified as the specific support given to LRRH, which included supplemental supplies for treatment and diagnostics when items were out of stock or unavailable. The program also provided extra staff to complete the time-intensive treatment and follow-up with hospitalized CM patients. These staff also provided outpatient follow-up care for patients for up to two years or until CD4 count reached >200. The outputs include daily medications and assessments as well as routine laboratory monitoring, lumbar punctures, and education. Another output is the essential medication support the hospital provided for CM during the CM-DTP. The logic model of change focuses on the change objectives that are related to behavioral and environmental outcomes, and determinants of the program. Only one behavioral and one environmental change objective is listed in Figure 1.7, but more objectives are possible. Although the key outcomes for the CM-DTP were improved diagnosis and decreased mortality, there were also secondary outcomes: improved CM care and decreased morbidity.

The evaluation incorporated the implementation of the CM-DTP, which involved participation from patients, staff, and the hospital. Each of these groups had specific activities and decisions they made to participate in this program. These decisions and actions were identified through specific questions, guided by the constructs of the IBM theoretical model. The primary outcomes of improved diagnosis and decreased mortality were analyzed and compared within each cohort and between cohorts. Secondary outcomes of improved CM care and were also analyzed. The impacts of the CM-DTP addressed several constructs of the IBM model through the improvement of knowledge, agency, salience of behavior, and environmental constraints, as well as improvements in mortality and morbidity.

Figure 1.8. Step 6 Logic Model



Dissertation Summary

This dissertation includes five chapters, three of which have been prepared as manuscripts, focusing on 1) a program evaluation of the CM-DTP, 2) patient and family member's experience of barriers and facilitators of CM care, and 3) healthcare provider's experience with the barriers and facilitators of providing CM diagnosis, treatment, and care to patients. The overall aims of this research were to evaluate the effects of a CM diagnosis and treatment program implemented at a rural referral hospital in Uganda and to determine how the program and overall CM care can be improved in rural Uganda. In working to explore the experiences of patients, we utilized surveys and interviews with patients and family members to gain their perspectives regarding their experiences with CM and the CM-DTP. Additionally, healthcare providers who were not a part of the CM-DTP but referred CM patients to LRRH from lower-level health centers were surveyed and interviewed about their knowledge and experience in order to identify barriers and facilitators to diagnosing and treating CM. Implementing these qualitative methods provided greater understanding of how CM care is sought, diagnosed, and treated and how it contributes to overall CM diagnosis, treatment, care, and mortality outcomes.

Chapter 1 includes an overview of the background of CM, review of literature, preliminary work of the CM-DTP, the theoretical model, and evaluation framework used for the evaluation of the CM-DTP.

Chapter 2 is an overview of the evaluation of the CM-DTP which analyzed the improvements this program made in CM care (Aim 1a & 1b) and assessed whether or not the program improved CM diagnosis and decreased mortality. Hospital charts and clinical record forms (CRFs) were reviewed to compile the database used for analysis. Comparisons with a historical cohort were used to evaluate the effects of the program. Predictors and other associated factors of mortality were also assessed.

Chapter 3 findings provide an understanding of how patients and family members of deceased patients experienced CM and the CM-DTP at LRRH (Aim 2). Issues related to knowledge, health-seeking behavior, and barriers and facilitators to CM care were assessed using surveys and interviews. Results from this research provided novel information regarding which areas to prioritize when working to improve CM care.

Chapter 4 results gives critical information about the barriers and facilitators encountered by healthcare providers at their local health centers (Aim 3). Surveys and interviews revealed barriers and facilitators related to CM education, knowledge, patient education, stigma, diagnosis, and treatment. This information helped confirm the findings from previous studies related to care with CM patients and supported findings from chapters 2 and 3.

Key findings are summarized, and recommendations are outlined in Chapter 5. Common themes were extracted and synthesized from the insights from the research described in Chapters 2, 3 and 4. Recommendation and improvements for the program are presented and nursing implications and future research topics are outlined and discussed.

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CHAPTER 2: Improving Cryptococcal Meningitis Outcomes: Evaluation of a Cryptococcal Meningitis Diagnosis and Treatment Program in Rural Uganda

ABSTRACT

Introduction: In rural Uganda, the accessibility and affordability of cryptococcal meningitis (CM) diagnosis and treatment is limited. In 2017, a Cryptococcal Meningitis Diagnosis and Treatment Program (CM-DTP) provided medications, diagnostics, supplies, and study staff at Lira Regional Referral Hospital. The program goals were to improve CM mortality by improving diagnosis, treatment, and care and identifying barriers to care.

Methods: We evaluated the effect of a CM-DTP over a two-year period (2017-2019; cohort 2) compared to a historical control (2015-2017; cohort 1) on outcomes of diagnosis and mortality among patients with meningitis symptoms. Hospital charts and clinical record forms were used to extract information related to diagnoses, treatments, and outcomes. Analyses were conducted using Chi-square test or Fisher's Exact test, Independent Student's t-test, and multivariate logistic regression.

Results: The median ages were similar between cohorts at 36.5 and 35.3 years, with most patients being male (64.6% vs. 62.6% in cohort 1 and 2, respectively). The number of confirmed cases of CM doubled (48 vs. 99) between cohort 1 and 2 ($p<0.001$). Mortality decreased among patients with confirmed CM in cohort 2 (41.4%) compared to cohort 1 (54.2%) but was not significantly different ($p=0.20$). The mean number of lumbar punctures (LPs) per patient increased in cohort 2 compared to cohort 1 (2.58 vs. 1.13, $p<0.01$). Lastly, antibiotic utilization differed significantly between cohorts, with fewer participants prescribed >2 antibiotics in cohort 2 versus cohort 1 (16.05% vs. 63.6%, $p<0.001$).

Conclusion: Implementation of the CM-DTP resulted in improved CM care as evidenced by improved diagnosis of CM leading to increased use of antifungal therapy, therapeutic LPs, and decreased use of antibiotics Further investigation is needed to determine the true effects of the program interventions on mortality and morbidity when a larger sample is collected through this on-going program.

Keywords*:* Cryptococcal meningitis, HIV/AIDS, program evaluation, rural Africa, mortality outcomes

INTRODUCTION

Cryptococcal meningitis is an infection of the brain which causes neurological symptoms such as headache, fever, neck pain, and stiffness.[1] Without proper treatment, this disease is fatal,[2] and it is most commonly seen in people with compromised immune systems, such as HIV/AIDS[3] patients with poorly controlled viral loads due to non-adherence or treatment failure. In 2016, Uganda implemented the test and treat program for HIV, which provided free testing and immediate start of antiretroviral (ARV) medication after screening for TB.[4] Despite ARV availability and most people living with HIV having started on ARVs, there continues to be an influx of new CM cases in sub-Saharan Africa. Many CM studies conducted in sub-Saharan Africa have shown that with appropriate screening, diagnosis, and treatment, deaths from CM can be prevented.[5-9]

In Uganda, the burden of CM disease in rural areas is not well understood. Unlike some urban areas of Uganda, rural areas face issues with limited resources and availability of appropriate diagnostic testing, drugs, and affordable treatment and supplies. Urban sites for CM management have more opportunities for research on novel diagnostics and treatments compared to rural areas which have a smaller population density, despite the fact that the majority (59.8%) of people living in sub-Saharan Africa live in rural areas.[10] CM care in Kampala (capital of Uganda) is managed at the national referral hospital, which is well supplied with treatments and diagnostics, including cultures and other supplies for CM care. However, the majority (76.23%) of those living in Uganda reside in rural areas[11] and face limitations due to shortage of supplies and availability of diagnostics and treatments. Without available diagnostics, CM is diagnosed by clinical manifestations and can be misclassified as other diseases and treated empirically, which may or may not improve patient outcomes. Without definitive diagnoses, the true burden of CM disease is unknown, and inadequate treatment is given.

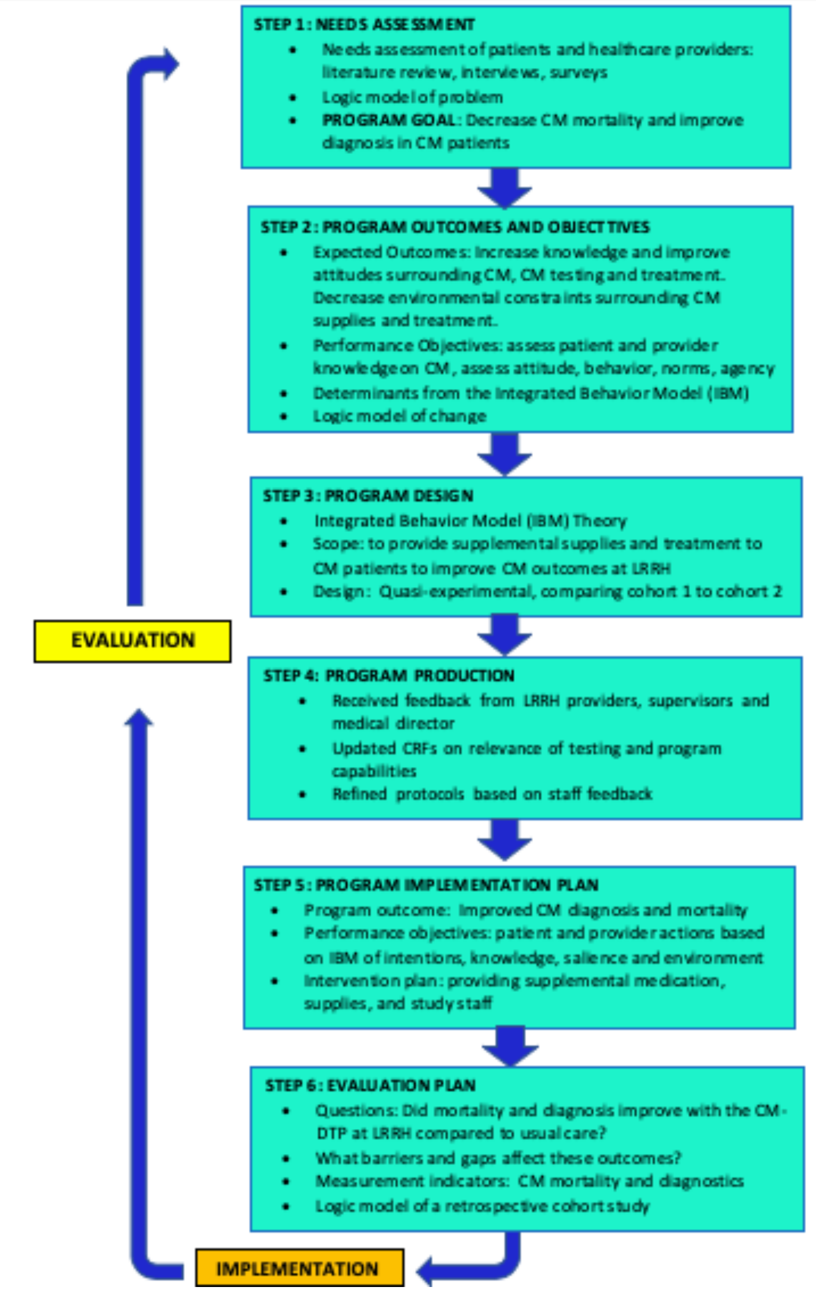
An assessment of usual care at Lira Regional Referral Hospital (LRRH) conducted in 2017 revealed that diagnosis for CM was only available for patients who could afford testing at outside laboratories, as the hospital was unable to test for CM as a result of having insufficient supplies. The primary treatment offered at that time was monotherapy with fluconazole, which is an inferior treatment for CM compared to combined treatment with amphotericin B and fluconazole.[12-14] Frequently, combined treatment with IV amphotericin B and fluconazole was only available when patients or families paid for the medications. If they were unable to pay, neither treatment nor diagnoses were given until they were able to raise the money. For many patients with CM, treatment was delayed or interrupted if finances were limited, leading to increased mortality among this population. These findings prompted the development of a CM Diagnosis Treatment Program (CM-DTP) at LRRH which was designed to improve the diagnosis and treatment of CM in order to improve survival and morbidity. This program was initiated in February of 2017 through a collaboration between LRRH, the Infectious Diseases Institute at Makerere University, and the University of Minnesota and provided diagnostic testing for CM and treatment with the recommended combination of Amphotericin B and fluconazole. All patients who were diagnosed with CM during this period were provided with treatment and monitoring at no additional cost. After two years of on-going program implementation, we evaluated the impact of the CM-DTP on diagnosis, treatment, and mortality outcomes of patients compared to a historical cohort of patients who were seen two years prior to program initiation.

METHODS

Evaluation Framework

We used the Intervention Mapping (IM) framework to evaluate the program goals of CM-DTP at LRRH to improve CM diagnosis and treatment and thereby decrease mortality (Figure 2.1). It applies social and behavior science theories for planning, implementing, and evaluating health programs.[15] There are six steps to this framework, which are iterative, and as information is gained, it can inform previous steps and provide new perspectives of current steps.[16,17] For this evaluation, we utilized steps 2, 3, 5, and 6 from this framework, as steps 1 and 4 were previously conducted. The theoretical model used for this evaluation was the Integrated Behavioral Model (IBM), which incorporates three key

Figure 2.1. Intervention Mapping Framework (Adapted by Bartholomew, et al., 2016)



theoretical constructs of attitude, perceived norms, and personal agency with other factors such as the environment, habit, knowledge, and salience of the behavior which affect behavior.[18] This model was used to guide the identification of the environmental and behavior determinants of this program evaluation. Additional information about the IBM or IM framework can be found in Chapter 1.

Study Design

This retrospective cohort study was used to examine the effect of usual care and CM-DTP on diagnosis, treatment, and mortality outcomes. This study utilized secondary data obtained from existing hospital records and clinical record forms (CRFs) designed for the CM-DTP. It compared two patient cohorts who were treated for CM from February 2015-February 2017 and from February 2017-February 2019. Cohort 1 was a historical cohort, in which patients who presented with signs and symptoms of meningitis were exposed to usual or routine care (2015-2017), while most patients in cohort 2 participated in the CM-DTP and received program treatment (2017-2019).

Ethics Approval

Regional ethics approval was obtained from Gulu University Research Ethics Committee (GUREC), Uganda National Council of Science and Technology (UNCST), and the University of Washington Institutional Review Board for the use and accessibility of secondary data. Patient consent was not required to access hospital records and CRFs.

Setting

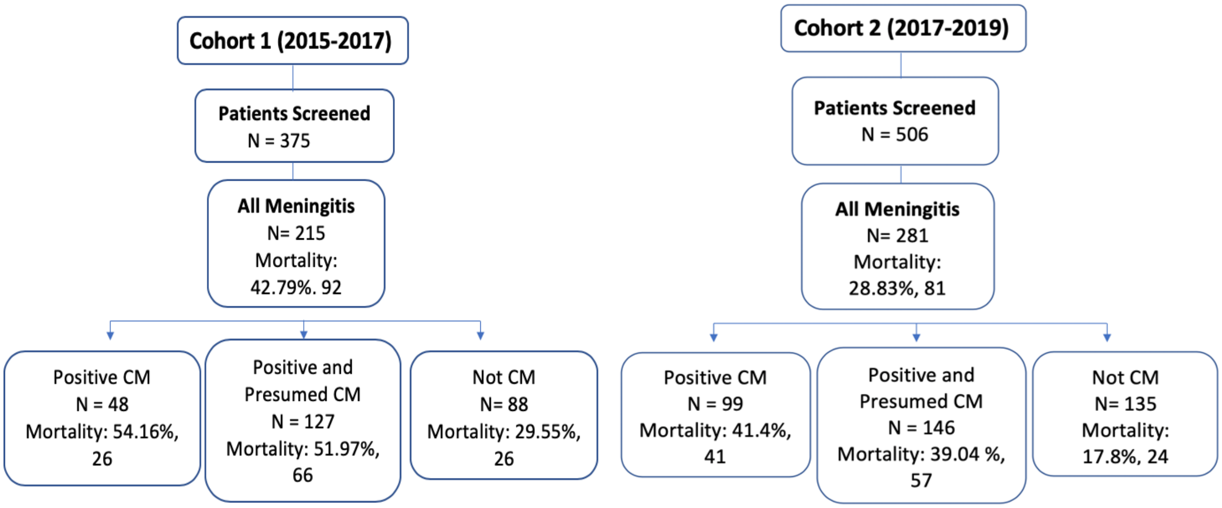
LRRH is located in rural, northern Uganda, an area which was occupied by the Lord's Resistance Army (LRA) from 1987 to 2006.[19] During this occupation, the area was often cut off from the rest of the country and the resources for healthcare were scarce. Currently, LRRH admits 1300 patients each month onto their wards from nine surrounding districts. The hospital provides specialty services in pediatrics, surgery, ophthalmology, psychiatry, maternity and palliative care.[20] The specialized services and improved resources are what bring patients from smaller health centers in for care.

Sample and Inclusion Criteria

Identification of Patients With Meningitis of All Causes

Retrospective chart reviews between February 2015-February 2019 were conducted on all patients age ≥8 admitted to LRRH and diagnosed with either any type of meningitis or CM or who had symptoms of headache in combination with one or more of the following: fever, confusion, photophobia, neck pain/stiffness, seizure, or a Glasgow coma scale (GCS) <14. In-depth chart reviews were conducted to determine whether patients could have had CM or meningitis based on diagnostic testing or clinical presentation, if no diagnostic testing was conducted. Charts where a diagnosis of meningitis was ambiguous were discussed by a panel that included medical officers, the site supervisor, and the study team to determine if they should be included. If consensus was not reached among this panel, the site supervisor made the final decision for chart inclusion. Through this process, we screened 375 charts in cohort 1 and 506

Figure 2.2. CM-DTP Sample Comparisons Per Cohort



charts in cohort 2 with potential meningitis, and we identified 216 patients in cohort 1 and 281 patients in cohort 2 who had meningitis, after excluding those who were unlikely to have had meningitis because alternative diagnoses were identified (Figure 2.2).

Identification of Patients With Laboratory Confirmed Diagnosis of CM

Among the patients identified with meningitis of all causes, 50 patients in cohort 1 and 104 patients in cohort 2 had laboratory confirmed CM. For cohort 1, patients were considered to have confirmed CM if they had a documented positive CrAg test, CSF India ink, or CSF gram stain positive for yeast. For cohort 2, a CrAg LFA test (Immy Inc., Norman, Oklahoma)[21] was performed on blood serum or CSF was utilized for CM diagnosis. This test was not available at the time that patients were seen in cohort 1. Seven patients with positive CM testing were excluded (cohort 1: n=2 and cohort 2: n=5) because they were HIV negative (cohort 1: n=1 and cohort 2: n=3) and admitted for less than two days with no documented treatment for CM (cohort 1: n=1 and cohort 2: n=2). After these exclusions, our total study sample included 48 patients in cohort 1 and 99 in cohort 2.

Identification of Patients With Presumed CM

We recognized for both cohorts that not all patients with CM received appropriate diagnostic testing and the diagnosis of CM was often made based on clinical presentation and impressions. For patients in cohort 1, failure to perform diagnostic testing usually occurred because patients were unable to afford testing or diagnostic testing was not available. To adjust for this, we presumed patients to have CM if they had a clinical diagnosis of CM recorded in the chart and antifungal treatment for CM. For some analyses, we utilized the group of positive and presumed CM, which included 127 (48 positive, 79 presumed) patients in cohort 1 and 146 (99 positive, 47 presumed) in cohort 2.

Measures /Instruments

For patients in cohort 2 who participated in the CM-DTP, hospital charts and CRFs were used to collect specific data. The CRFs extracted data on diagnosis, symptoms, symptom days, treatments, medical history, physical exams, laboratory results, outcomes, HIV and ART status, complications, diagnosis, treatment, and mortality outcomes. We also identified demographic characteristics of patients, symptoms days, and ART and HIV history. For cohort 1, hospital charts were reviewed on all patients included in the study who did not participate in the CM-DTP. The information from the hospital charts extraction was similar to what was obtained in the CRFs to maintain data continuity.

Procedure

Hospital charts of all patients who met sampling criteria and were admitted to LRRH between February 2015-February 2019 were reviewed, along with previously collected CRF forms from the CM-DTP. A database was developed to collect specific information for data extraction from patient charts and CRFs. This database was used to analyze the information which was logged with data validation on each data point with a second person. A codebook was developed to provide continuity of data codes between data entry personnel. Data regarding demographics, symptoms, physical assessments, treatments, diagnostic tests, complications or adverse events, outcomes, and HIV and ART history were transcribed into this database for analysis.

Outcomes

The key outcomes for the CM-DTP were improved diagnosis and decreased mortality. Secondary outcomes focused on improved CM care and decreased morbidity. Morbidity outcomes were defined as complications of blindness, deafness, and cognitive dysfunction (e.g.

confusion, hallucinations, mental sluggishness, seizures), as well as treatment complications (identified as vomiting, renal insufficiency quantified by creatinine level of <1.2 mg/dL for women and <1.4 mg/dL for men,[22] hypokalemia identified as potassium <3.mmol/L[23] and anemia classified by a hemoglobin of <10 g/dL based on WHO guidelines).[24] These outcomes were analyzed within each cohort and between cohorts to determine whether differences were observed after the implementation of the CM-DTP.

Analyses

Descriptive statistics were used to calculate means and proportions on demographic information, admission and discharge diagnoses, baseline neurologic status, symptoms, complications, and treatments. Means and proportions were used to: 1) quantify symptoms and days of hospitalization, 2) specify the types of treatment and CM care provided, and 3) compute treatment outcomes of mortality and morbidity (defined as complications of blindness, deafness, anemia, hypokalemia and renal insufficiency which occurred during disease progression or treatment).

To determine significant relationships between the two cohorts, a Chi-square test or Fisher's Exact test was performed for categorical variables based on whether observed cells were less than 10. Student's t-test was used for comparisons of continuous variables in the analysis. For mortality outcomes in cohort 2, we conducted Fisher's Exact test to analyze each covariate of CM treatment type (antifungals, antibiotics, LPs), previous CM diagnosis, CD4 count, symptoms, and morbidity variables to determine which variables were predictive of mortality. Logistic regression was used to compare mortality and continuous covariates. Hypothesis testing was two-sided with a significance level of 0.05. All analyses were performed using R version 3.6.0.[25]

RESULTS

Characteristics of CM Patients Before (Cohort 1) and After (Cohort 2) Implementation of the CM-DTP

Demographics

Demographic information for patients with laboratory confirmed CM was similar between cohorts 1 and 2 with respect to age (36.5 vs. 35.3 years), male gender (64.6% vs. 62.6%) and HIV positive status (100% in both cohorts) (Table 2.1). There were differences related to ART history and current ART status, with cohort 1 having more people taking ART (75% vs. 65.9%) and cohort 2 having more patients with a history of ART use than cohort 1 (92.9% vs. 77.1%). Despite cohort 1 having more people on ART, they had lower mean CD4 counts (79.6 ± 92.8) compared to cohort 2 (166.3 ± 207.5), which may suggest recent commencement of ART treatment, lack of ART adherence, or treatment failure.

Table 2.1. Demographics of Cohorts 1 and 2

	Cohort 1 2015-2017	**Cohort 2 2017-2019**
All Meningitis	**N = 215 (N (%))**	**N =281 (N (%))**
Age (mean, SD)	33.6, ±14.2	35.6, ±13.5
Gender (Male)	93 (43.3%)	139 (49.5%)
Documented HIV Positive	129 (60.0%)	234 (83.3%)
Meningitis other than CM*	**N = 88 (N (%))**	**N = 135 (N (%))**
Age (mean, SD)	30.5, ±16.1	35.3, ±14.5
Gender (Male)	44 (50%)	77 (57.0%)
Documented HIV Positive	4 (46.6%)	90 (66.7%)
Positive CM	**N = 48 (N (%))**	**N = 99 (N (%))**
Age (mean, SD)	36.5, ±9.9	35.3, ±17.68
Gender (Male)	31 (64.6%)	62 (62.6%)
Documented HIV Positive	48 (100%)	99 (100%)
History of ART	37 (77.08%)	79 (92.9.%)
Receiving ART	36 (75%)	56 (65.9%)
CD4 Count (mean, SD)	79.6, ±92.8	166.3, ±207.5
Positive and presumed CM	**N = 127 (N (%))**	**N = 146 (N (%))**
Age (mean, SD)	36.7, ±10.8	36.2, ±12.4
Gender (Male)	49 (38.6%)	62 (42.5%)
Documented HIV Positive	125 (98.4%)	144 (98.6%)
History of ART	96 (75.6%)	113 (77.4%)
Receiving ART	92 (71.9%)	86 (58.9%)
CD4 Count (mean, SD)	68.8, ±74	182.6, ±218.6

*Other meningitis diagnoses: bacterial, viral, tuberculosis, and other clinically based diagnoses

Symptoms

Evaluation of the presenting symptoms on admission showed that vomiting and confusion were significantly different in cohorts 1 and 2. In cohort 1, 15 (75.0%) patients had vomiting compared to 44 (47.8%) patients in cohort 2 (p=0.05; Table 2.2). There were 18 (78.2%) patients who had confusion on admission in cohort 1 compared to 25 (28.4%) in cohort 2 (p=<0.001, CI: 0.03-0.36). Additionally, cohort 2 had longer mean symptom days (22.3, ±19.7) compared to cohort 1 (16.4, ±17.9) but was not statistically different (p=0.10). This finding provides evidence that there was a delay from the time of symptom onset to diagnosis and treatment of CM. The average days of symptoms were not significantly different between cohorts, but cohort 2 had longer delays to care compared to cohort 1. This finding also suggests lack of patient knowledge to seek care sooner for symptoms related to CM. Also, some patients from cohort 1 had delays in treatment due to inability to pay for diagnosis or treatment as evidenced by statements like “no drugs available,” “waiting for testing,” or “unable to afford treatment” written in their charts.

Table 2.2. Baseline Symptoms at Admission

Symptoms	**Cohort 1 N=48 (N (%))**	**Cohort 2 N=99 (N (%))**	**P-value**
Headache	41 (95.3%)	92 (93.9%)	>0.99
Fever	24 (82.8%)	84 (86.6%)	0.56
Vomiting	15 (75.0%)	44 (47.8%)	**0.05**
Confusion	18 (78.2%)	25 (28.4%)	**<0.001**
Nuchal Rigidity	20 (66.7%)	77 (79.4%)	0.22
Kernig’s Sign	16 (33.3%)	77 (77.8%)	1.00
CM History	5 (12.5%)	64 (64.6%)	0.09
TB History	8 (16.7%)	11 (11.1%)	0.39
Symptom Days (mean, SD)	16.4, ±17.9	22.3, ±19.7	0.10

Improved Diagnosis of CM After Implementation of the CM-DTP

Among all patients with meningitis, we evaluated the number who received diagnostic testing to evaluate for CM in cohorts 1 and 2. In cohort 1, 48 (22.2%) patients received CM diagnostic testing, whereas 99 (35.2%) patients received diagnostic testing for CM in cohort 2.

Thus, the number of diagnostic tests performed increased greatly for cohort 2 following implementation of the CM-DTP and was statistically different between cohorts (p=0.002) (Table 2.4). The type of diagnostic testing performed for patients in cohorts 1 and 2 is shown in Table 2.3.

In cohort 2, 90.9% of patients had positive CrAg LFA tests on CSF, 9.1% had positive CrAg LFA tests on blood, 51.5% had positive India ink test results and 47.5% had a positive gram stain for yeast. In comparison, among the patients in cohort 1, 68.8% had positive CSF CrAg latex agglutination (LA) tests, 27.1% had positive India ink tests, and 41.7% had positive CSF gram stains for yeast (Table 2.3). Overall, CM diagnoses improved in cohort 2 following implementation of the CM-DTP.

Table 2.3. CM Diagnostic Tests

Diagnostic Tests	**Cohort 1 (N (%))**	**Cohort 2 (N (%))**
CSF CrAg Test	33Ψ (68.8%)	90* (90.9%)
Blood CrAg	15Ψ (31.2%)	9* (9.1%)
India Ink Test	13 (27.1%)	51 (51.5%)
Gram Stain Yeast +	20 (41.7%)	47 (47.5%)

*Lateral flow Assay
Ψ Latex Agglutination

Improved Treatment of CM After Implementation of the CM-DTP

The type of antifungal treatments ordered were similar between cohort 1 and 2 within the confirmed positive CM group. The most common antifungal treatment of combination Ampho B and fluconazole showed that cohort 1 and cohort 2 had similar treatment percentages at 83.3% and 89.9% which indicated that the Uganda CM Guidelines were followed closely by providers in both cohorts (Table 2.4). In contrast, treatments among the positive and presumed group were significantly different, as those in cohort 1 had 40.9% of patients treated with combination Ampho B and fluconazole compared to 61% patients in cohort 2 (p=0.001). This finding revealed that overall, prescribing of combination antifungal treatment improved in cohort 2 compared to cohort 1.

The CM-DTP Led to Decreased Mortality Outcomes

The data extraction between the two cohorts found three distinct groups which emerged from the data: 1) confirmed positive CM, 2) positive and presumed CM, and 3) all meningitis patients. Mortality was analyzed within each of these groups, comparing the two cohorts to understand the effects that occurred with the introduction of the CM-DTP. We found that the overall mortality across all groups decreased in cohort 2 when compared with cohort 1 (Table 2.4). In our primary group, the positive confirmed CM patients in cohort 1 had 51.2% mortality compared to 41.4% in cohort 2, which showed an overall decrease in mortality; however, this difference was not significant between cohorts (p=0.20). The lack of significance could be related to the small sample size in each cohort, but the finding was suggestive of the effects of

Table 2.4. Impact of the CM-DTP on Mortality, Diagnosis and Treatment

POSITIVE CM	**COHORT 1 2015-2017**		**COHORT 2 2017-2019**		
Mortality	**Patients**	**Deaths (N (%))**	**Patients**	**Deaths (N (%))**	**P-value**
Positive CM	48	26 (54.2%)	99	41 (41.4%)	0.20
Positive & presumed CM	127	66 (52.0%)	146	57 (39.0%)	**0.04**
All meningitis	215	92 (42.8%)	281	84 (28.8%)	**0.04**
Meningitis other than CM	88	26 (29.6%)	135	27 (20.0%)	0.14
Diagnosis	**Patients**	**%**	**Patients**	**%**	**P-value**
Positive CM diagnoses	48	22.2%	99	35.2%	**0.002**
All cases of meningitis	216		281		
Treatment	**Patients**	**%**	**N**	**%**	**P-value**
Ampho B and fluconazole	40	83.3%	89	89.9 %	0.38
All cases of positive CM	48		99		
Treatment with antibiotics	44	91.7%	78	78.8%	0.06
All cases of positive CM	48		99		
Treatment with LP	33	68.8%	92	92.9.0%	**<0.001**
All cases of CM	48		99		
	Patients	**Mean, SD**	**Patients**	**Mean, SD**	**P-value**
Number of LPs	39	1.10, ±0.54	246	2.24, ±1.14	**<0.001**
All cases with LPs	33		92		

the program (diagnosis, treatment, and monitoring), which improved mortality. Additionally, those in the positive and presumed group had significant differences in mortality between the two cohorts (52% vs. 39%, p=0.04). Although some patients were not identified with CM in this group, access to appropriate treatment may have improved mortality outcomes among those in cohort 2. Lastly, for those in the all meningitis group, mortality was significantly different between cohort 1 (42.8%) and 2 (28.8%, p=0.04).

Predictive or Associated Factors of CM Mortality

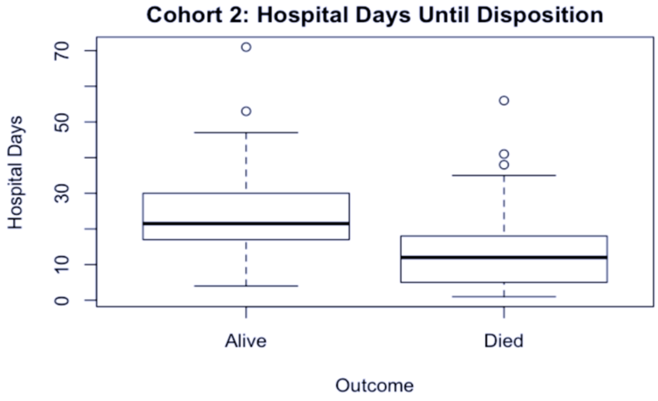
Confusion and GCS <15 Were Predictive of CM Mortality

In the analysis of predictors of death, we found that symptoms of confusion and a GCS <15 were significant predictors. Presence of confusion at admission had 3.5 times the odds of death compared to those who did not have confusion (p=0.02, CI: 1.22-10.65; Table 2.5). Additionally, those who had a GCS <15 had increased odds of death compared to those who had a normal GCS of 15 (OR: 4.28, p=0.001, CI: 1.63-11.9).

Length of The Hospital Stay Was Associated With CM Mortality

Among CM positive confirmed patients who died in cohort 2, the mean number of days spent in the hospital was 13.68, compared to 24.07 days among those who lived. This finding showed that those who lived had a longer hospitalization than those who died (Table 2.2). The analysis of hospital days on mortality found that longer hospital stays were significantly associated with lower odds of death compared to those who stayed in the hospital a

Figure 2.3. Cohort 2 Hospital Days and Death



shorter time when controlling for illness severity, identified as a GCS <15 (OR: 0.9, p=0.002; Table 2.5). This coincides with the boxplot in Figure 2.3, which illustrates that those who died, died earlier in their hospitalization compared to those who survived.

Table 2.5. CM Positive Cohort 2, Factors of Morality

COHORT 2 POSITIVE CM MORTALITY	**N (%)**	**Death (%)**	**OR**	**P-value**	**CI**
Vomiting	44/92 (47.8%)	19/44 (43.2%)	1.16* 1.43Ψ	0.73* 0.45Ψ	0.51-2.66* 0.56- 3.63Ψ
No Vomiting	48/92 (52.2%)	19/48 (39.6%)	1		
Confusion	25/88 (28.4%)	16/25 (64%)	**3.60**	**0.01**	**1.35-9.38**
No Confusion	63/88 (71.6%)	21/63 (33.3%)	1		
GCS <15	45/91 (49.5%)	26/45 (28.6%)	**4.28**	**0.001**	**1.63-11.90**
GCS =15	46/91 (12.1%)	11/46 (12.1%)	1		
Any Antifungal	93/96 (96.9%)	38/93 (40.6%)	0	0.07	0-1.77
No Antifungal	3/96 (9.4%)	3/3 (100%)	1		
Antibiotics >2	13/81 (81.3%)	7/13 (53.8%)	1.77* 2.46Ψ 3.82‡	0.35* 0.19Ψ 0.08‡	0.54-5.85* 0.63-9.56Ψ 0.86-16.96‡
Antibiotics ≤2	68/81 (84.0%)	27/68 (39.7%)	1		
Any Morbidity	23/27 (85.2%)	12/23 (52.2%)	1.09	1	0.07-17.4
No Morbidity	4/27 (14.8%)	2/4 (50%)	1		
People with lumbar punctures	92/95 (96.8%)	39/92 (42.4%)	0.37	0.58	0.006-7.38
People with No lumbar punctures	3/95 (3.2%)	2/3 (75%)	1		

	Mean, SD	**OR**	**P-value**	**CI**
Lumbar punctures	2.24 (1.14)	**0.64*** **0.62Ψ** 0.80‡	**0.02*** **0.03Ψ** 0.36‡	0.44-0.92* **0.39- 0.96Ψ** 0.49- 1.30‡
Symptom days	19.15 (16.53)	0.99	0.26	0.97-1.01
Hospital days	13.68 (11.88)	**0.91*** **0.92Ψ**	**<0.001*** **0.002Ψ**	**0.87-0.96*** **0.87-0.97Ψ**
CD4	113.41 (136.47)	0.99	0.59	0.99-1.00

* Unadjusted logistic regression (LR)
Ψ LR Adjusted for GCS
‡LR Adjusted for GCS and hospital days

Lumbar Punctures Were Associated With CM Mortality

The total number of people who had an LP procedure performed in cohort 2 was 92 (92.9%), and 42.4% of those who received an LP died, compared to 75% who died without an LP being performed (Table 2.5). The average number of LPs performed increased between cohorts with an average of 1.18 LPs in cohort 1, compared to 2.67 LPs in cohort 2 and was significant (p <0.001) using the Student's t- test (Table 2.4). Confounding effects of hospital days and illness severity were identified, as patients stay longer in the hospital and become sicker, the likelihood of having more therapeutic LPs increases. To control for these confounders, a multivariate logistic regression analysis was conducted to determine the association of LPs with mortality in cohort 2. This analysis found that the number of LPs after controlling for GCS and hospital days was not significantly different between those who lived and died (p=0.36), and that those who had more LPs had lower odds of death compared to those who had fewer LPs (OR 0.80 CI: 0.49-1.30).

Combination Antifungals Were Not Associated With CM Mortality

The most commonly prescribed antifungal mediation was a combination of Ampho B and fluconazole in both cohorts (83.3%, 89.9%), which is the recommended treatment for CM based on Uganda Clinical Guidelines (Table 2.4). Although combination treatment increased in cohort 2 from cohort 1, no significant differences were found between cohorts with any of the antifungal medications (Table 2.6). Additionally, the use of any antifungal was not significantly associated with mortality in cohort 2 (p=0.07) and most likely due to the small comparison group, as only 9.4% (n=3) of patients had no antifungal treatment (Table2.5).

Antibiotics Were Not Associated With CM Mortality

The number of antibiotics which were typically ordered during the hospitalization ranged from zero to four. The overall number of patients who had antibiotics ordered decreased between cohort 1 and 2, as 44 (91.7%) patients in cohort 1 were prescribed antibiotics compared to 78 (78.8%) patients in cohort 2 (Table 2.4). These differences, however, were not significant (p=0.06). When antibiotics were categorized into two groups (≤2, >2), we found that the number of antibiotics prescribed between cohorts differed significantly, with cohort 1 having a higher number of >2 antibiotics ordered compared to cohort 2 (63.6% vs. 16.05%, p< 0.001; Table 2.6). In contrast, the number of those who were ordered ≤2 antibiotics was higher in cohort 2 than cohort 1 (84% vs. 36.4%) and was found to be significantly different (p<0.001). Among those who died in cohort 2 of the CM positive confirmed group, we found that those who had >2 antibiotics had increased odds of death (OR: 3.82, CI:0.86-16.96) after controlling for the confounders of disease severity (GCS <14) and hospital days. This finding, however, was not significantly associated with mortality (p=0.08; Table 2.5).

Table 2.6. Medication Treatment Comparison Between Groups and Cohorts

CM POSITIVE MEDICATIONS	**Cohort 1 Received**	**Cohort 2 Received**	**P-value**	**Cohort 1 Died**	**Cohort 2 Died**	**P-value**
ANTIFUNGALS	N=48	N=99		N=26	N=41	
No Treatment	1 (100%)	3 (3%)	>0.99	1 (100%)	3 (100%)	>0.99
Ampho B Only (%, N)	2 (4.2%)	2 (2%)	0.60	1 (50%)	2 (100%)	>0.99
Fluconazole Only (%, N)	6 (12.5%)	5 (5.1%)	0.18	2 (33.3%)	2 (40%)	>0.99
Combo Ampho B and fluconazole (%, N)	40 (83.3%)	89 (89.9%)	0.29	23 (56.4%)	34 (38.2%)	0.06
ANTIBIOTICS	**N=44**	**N=81**	**P-value**	**Cohort 1 Died**	**Cohort 2 Died**	**P-value**
≤2	16 (36.4%)	68 (84%)	**<0.001**	6 (37.5%)	27 (39.7%)	>0.99
>2	28 (63.6%)	13 (16.05%)	**<0.001**	1 (60.7%)	7 (53.8%)	>0.99

Morbidity Was Not Associated With CM Mortality

A total of 25 patients (25.3%) had at least one morbidity outcome and 8 (32%) died in cohort 2 (Table 2.5). Morbidity variables were identified as cognitive dysfunction, vomiting, renal insufficiency, hypokalemia, anemia, hearing and vision loss. Among cohort 2, there were 53 documented morbidity complications over the course of the hospitalization (Table 2.7). The most common complications were anemia with 19 (19.20%) patients, followed by cognitive dysfunction at 16 (16.20%) patients. Those who had complications with renal insufficiency had the highest probability of mortality at 100%, while those with hearing and episodes of morbidity complications, with some patients experiencing multiple morbidities over vision loss, had 50% probability of mortality. No morbidity data was available for cohort 1 due to insufficient data from chart extractions. Analysis on the association of morbidity with mortality found that those who had morbidity had lower odds of death compared to those who had no morbidity (OR: 0.71, CI: 0.12-4.45); however, this was not a statistically significant association (p=0.71). The true number of those who had no morbidity was underestimated, as only 10 patients had "no morbidity" documented, while 64 patients had missing data related to this outcome.

Table 2.7. Morbidity Factors Related to Mortality in Cohort 2

Morbidity	**Cohort 2 N=99**	**%**	**Deaths N=21**	**Death %**	**P-value**
Hearing loss	4	4.04%	2	50%	1.00
Vision loss	2	1.01%	1	50%	1.00
Renal insufficiency	2	2.02%	2	100%	0.15
Hypokalemia	10	10.10%	3	30%	0.72
Anemia	19	19.20%	6	31.6%	0.40
Cognitive dysfunction	16	16.20%	7	43.8%	0.76

DISCUSSION

For this study, we analyzed a CM diagnosis and treatment program which aimed to improve CM care, diagnosis, mortality, and morbidity. The findings from this study showed that this program led to improved diagnosis and treatment of CM, which were both associated with improved mortality. This knowledge also highlighted which areas of the CM-DTP should be enhanced to improve collaboration with LRRH in order to increase the program's impact in saving the lives of patients with CM.

CM Diagnosis

The findings from this study showed that the CM-DTP significantly increased the number of CM diagnoses, as 35.2% of all meningitis cases in cohort 2 were identified as CM compared to 20.4% in cohort 1. Comparing which diagnostic tests were used to identify CM, 91% were tested with a CSF CrAg test in cohort 2 compared to 69% in cohort 1. This test is the most appropriate test to use because of its timely results (10 minutes)[21] and high sensitivity and specificity compared to India ink or culture. It is also the preferred test for CM diagnosis and is recommended by the WHO.[26] The long-standing gold standard for CM diagnosis is CSF culture,[27] but this test is not available in Lira or in many other areas of SSA. Furthermore, it is expensive and time-consuming for samples to be transported to Kampala or other facilities for culture. There are two major types of CrAg testing that were used at LRRH for CM diagnosis: the LA test, which is performed in a clinical laboratory and requires specialized equipment, and the LFA test, which was introduced through the CM-DTP and is an inexpensive test that can be performed rapidly at the bedside. The LFA test has a 99.3% sensitivity and 99.1% specificity,[28,29] and the LA test has a sensitivity of 97-97.8% and specificity of 85.9-100%.[30] Due to its higher sensitivity and specificity and its ease of use, the CrAg LFA is now considered the new "gold standard" for CM diagnosis.[31,32] In cohort 1, the LFA test was not readily available and CrAg tests were performed predominantly through LA testing. The latter test was less sensitive and specific, which may have led to more false test results, leading to potential misdiagnosis in cohort 1 and/or greater uncertainty of the test results among providers.

Additionally, our chart reviews showed that many patients were treated for CM empirically based on a clinical diagnosis without laboratory testing to confirm it. For cohort 1, we found a two-fold increase in the number of patients treated for CM when comparing laboratory confirmed CM to all who were treated for CM (confirmed positive CM and presumed CM). Overall, the identification of CM cases improved with the CM-DTP, as cohort 1 had 79 (62%) of CM cases that were diagnosed and treated for CM without laboratory confirmation, and cohort 2 had only 47 (32%) cases where CM was treated without laboratory confirmation. However, the true number of CM cases in each cohort remains unknown given the incomplete uptake of CM testing, though there was significantly more testing performed in cohort 2.

We also observed missed opportunities for CM diagnosis and program enrollment of patients in cohort 2, as evidenced by the 47 people in our sample. This could be attributed to the lack of awareness of the CM-DTP in the early months of program initiation among the different departments at LRRH and surrounding health facilities and the resignation of the sole study nurse who worked weekends in April 2018. A new nurse was hired in mid-June 2018, resulting in a two-month gap in CM testing and screening over weekends. The missed enrollments may have contributed to issues related to missing data in cohort 2.

Treatments

Providers at LRRH were knowledgeable of the Ugandan guidelines for CM treatment even before the implementation of CM-DTP, as evidenced by the high rate of appropriate treatment of combination Ampho B and fluconazole; however, rates of appropriate treatment increased after its implementation. This may be due to recent education of LRRH providers, as the majority of providers are interns or medical officers recently out of medical school who had just been taught about the Ugandan CM Treatment Guidelines, more experience or frequent presentations of patients with CM, and study staff who oversaw the diagnosis and treatment of all the patients involved in the CM-DTP. Overall, the providers in both cohorts performed similarly in ordering antifungal medications; however, because of poor documentation of medications and treatments given, we were unable to confirm whether many of these patients actually received the medications that were ordered, especially in cohort 1. For cohort 1, results of our chart review revealed that some patients were unable to afford diagnostic testing or antifungal treatments and were, therefore, not fully treated for CM based on guidelines. Partial treatment for CM is not ideal. Researchers in Botswana found that missing even 1-2 doses of combination Ampho B and fluconazole treatment decreased the probability of survival significantly compared to those who did not miss any doses.[5] Those who had 1-2 missing doses over the first two weeks had 2.92 times the risk of death compared to those who had no missing doses ($p=0.01$), and at 10 weeks, the risk of death was doubled (HR: 2.06) among these two groups ($p=0.01$).[5] These findings highlight the importance of a full CM treatment course for patients in ensuring the greatest chance of survival.

Our analysis showed that antifungal prescriptions for those with confirmed CM were similar between the cohorts. There was, however, a significant difference in antibiotic prescriptions between cohorts. In cohort 1, more prescriptions of >2 antibiotics were ordered compared to cohort 2, and more providers in cohort 2 prescribed ≤2 antibiotics compared to cohort 1 providers. Having a definitive diagnosis of CM may have limited the number of unnecessary antibiotics to be ordered in cohort 2. However, more antibiotics were still prescribed in cohort 1 for those with a definitive diagnosis of CM. This difference may be due to the type of diagnostics used to determine CM. CrAg LFA testing is the best test choice due to its high sensitivity and specificity but was not available in cohort 1. We posit that in cohort 1, either a definitive diagnosis of CM through the available testing methods at the time was not definitive enough or illness severity was greater; therefore, more antibiotic therapy was ordered to treat other potential etiologies of illness. Intuitively, when a definitive diagnosis is made, superfluous medications or treatments are halted. In cohort 2, the utilization of an accurate diagnostic test using CrAg LFA may have contributed to the decrease in unnecessary antibiotic use, which can improve antibiotic stewardship and decrease costs for the hospital. Having a trusted and accurate diagnostic test for CM not only leads to appropriate treatment and therapy but also decreases unnecessary treatment, lowering the chances of creating antibiotic resistant pathogens and reducing costs for the hospital and patient. No other studies that focused on CM treatments were able to be identified to support this finding of decreased antibiotic utilization.

Some treatments were unavailable during the program period when stockouts of antifungals and other treatment medications occurred because of local or nation-wide drug unavailability and payment reimbursement issues with the contracted pharmacy. These stockouts lasted anywhere from a few days to a few weeks. All efforts were made to get supplies quickly, and alternative pharmacies from within and outside of Uganda were sought to provide these medications. These intermittent stockouts may have impacted the outcomes for patients who were being treated during these times.

Mortality

The CM-DTP led to improved mortality. Although the improvement in mortality for laboratory confirmed CM in cohort 2 compared to cohort 1 (54.2% vs. 41.4%) was not statistically significant, there were significant improvements in mortality in those with presumed plus confirmed CM, as well as in all meningitis. The regrouping of cohorts by combining positive and presumed revealed a larger and more similar sample size between cohorts 1 and 2 (n=127 vs. n=147), with cohort 2 having more diagnoses of CM compared to cohort 1. This regrouping also found significant differences in mortality with 51.90% and 39.04% in cohorts 1 and 2, respectively. Additionally, those classified in the all meningitis group included the positive and presumed cases and those who had a diagnosis of non-CM related meningitis. The differences in mortality between all meningitis cases in cohorts 1 and 2 were also significant (42.99% vs. 29.83%), with cohort 2 having fewer deaths. Reviewing mortality differences from the all meningitis and positive and presumed CM groups showed that the program may have had improved mortality outcomes through heightened awareness of meningitis symptoms, leading to more timely recognition and treatment of all types of meningitis. Also, for those who tested negative for CM, this ruled out CM and may have provided a default diagnosis of bacterial or other meningitis cause for those who could not afford further testing for their condition. These factors could be possible contributors in the improvement in mortality for patients in cohort 2.

Predictors and Associations of Mortality

Two significant predictors (confusion, GCS <15) and two significant associations (number of LPs and hospital days) of mortality were identified from our study. The finding of confusion and GCS <15 as a predictor of mortality in CM patients is supported by previous research. These studies found that altered mental status (which encompasses confusion and GCS <15) was a prognostic factor associated with mortality among people with CM.[33,34] The variables of hospital days and number of LPs are related to each other; as the number of hospital days increases, so, too, does the likelihood of having additional LPs performed, leading hospital days to be a confounder on LPs. Additionally, confusion and GCS <15 were also confounders with LPs, since they are indicators of illness severity (typically, more LPs are performed when increased confusion occurs or when GCS decreases). We were able to control for these confounders in our analysis by including these covariates in our logistic regression model. Another important discussion is the condition of multicollinearity with confusion and GCS <15, as confusion is a component of a GCS score and is not an independent coefficient. To control for this, we only used GCS in our logistic model. After adjusting for confounders, an increase in the number of LPs had lower odds of death among patients in the CM-DTP but was not significantly associated with mortality (OR: 0.80, CI: 0.49-1.30, p=0.36).

Much research has been done on the effects of therapeutic LPs in patients with CM. The addition of therapeutic LPs to a patient's treatment plan has been shown to improve mortality outcomes in addition to increasing comfort.[34] Current guidelines for therapeutic guidelines are in place with some suggesting daily therapeutic LPs, while others predicate LPs on CSF pressure. The WHO advises continuing daily LPs if opening pressures are >20 cm H_20 with drainage of 20-25 ml of CSF.[27] Studies have shown improved mortality when patients have received routine therapeutic LPs during the course of induction therapy. One study from Tanzania showed mortality improvement from 46 to 75%,[35] while a study in Uganda and South Africa showed a reduction in mortality risk by 69% by implementing routine therapeutic LPs.[34] These studies support the findings from this study, which found that an increase in the number of LPs performed decreased the odds of death among patients who participated in the CM-DTP.

Impacts from IM Framework

On review of the impacts from this evaluation using the IM framework, we found that mortality decreased, CM diagnosis increased, financial burden for both patients and hospital decreased with the supplemental procurement of treatment and diagnostic supplies, and medical staff confidence and knowledge of current CM diagnosis and treatment protocols improved. Additionally, the hospital's supply request for CM diagnostics and treatment from the national medical stores have allocated these supplies for the CM-DTP when they are available. These findings were encouraging and showed the positive impacts this program had on CM care and, when collaboration with procurement is present, between LRRH and national medical stores.

Costs of the CM-DTP

The CM-DTP provided supplemental CM diagnostic, monitoring and treatment supplies, which were key components of this program. We found that through these interventions, patients who were unable to afford the appropriate diagnosis and treatment for CM were able to access this life-saving treatment and decreased both their costs for care and exposure to unnecessary antibiotics. CM-DTP decreased out-of-pocket costs for patients and for the hospital, as the program paid for supplies related to CM diagnostics, antifungals, and laboratory monitoring. However, the extent of these cost savings, as well as the costs to integrate this program as a hospital protocol, are unknown. We found that CM-DTP does improve CM mortality, but the long-term continuation of the program is dependent on whether the facility will be able to support these measures for CM care. Providing an economic evaluation will make it possible to calculate expenditure, cost-benefits, and cost-effectiveness analyses of this program so that hospital leaders can make an informed decision about their investment and support to maintain this program.

Studies conducting a cost-analysis on a similar program like the CM-DTP were not identified; however, cost analyses of CM screening programs have been conducted in the past. One such study in Vietnam found that implementing a screening program would cost $190 per life-year gained,[36] while a modeling study in Uganda found that treatment for patients who had a positive screen (non-CM disease) would cost \$32/disability adjust life year (DALY) gained and treatment for CM disease would cost \$75/DALY gained.[37] Providing similar information on the cost-effectiveness of the CM-DTP will help quantify the cost-savings of implementing this program versus not implementing to LRRH leadership.

Limitations

There were several limitations to our study related to the quality and strength of associations we are able to assign to our findings. In the confirmed positive CM group, we found a small sample size in both cohorts, which limited the analyses we were able to perform to determine which covariates of the CM program were associated with mortality. It also limited our ability to find statistically significant evidence of the key interventions of the CM-DTP which were associated with mortality. Additionally, because of missing data, evaluations of morbidity between cohorts were not conducted.

There was confounding when analyzing mortality to number of LPs. The confounding variables of hospital days and GCS were controlled for using multivariate logistic regression by incorporating these variables into the model. There may also have been confounding because of differences in availability of treatment between the two cohorts. In cohort 1 (usual care), patients were provided more expensive treatments, such as Ampho B, if they were able to afford these medications, while patients who were unable to pay likely received inferior treatments, such as fluconazole monotherapy or no therapy at all. Thus, financial status was a confounder to Ampho B treatment and mortality for cohort 1 patients. In contrast, all patients in cohort 2 who had confirmed positive CM received Ampho B, regardless of their ability to pay.

CONCLUSION

The evaluation of the CM-DTP provided evidence of decreased mortality through the interventions provided by the program and revealed several key areas of improvement in CM care and diagnosis. Specifically, the CM-DTP helped identify more CM cases, utilized highly sensitive and specific diagnostic testing with CrAg LFA, improved compliance to Ugandan clinical guidelines for CM treatment using Ampho B and fluconazole, increased the number of LPs performed per patient, and decreased the overall usage of antibiotics. These combined interventions resulted in a decreased trend of overall mortality. The CM-DTP is improving CM outcomes and should continue to be implemented.

Future research should include another evaluation with a larger sample, which may provide stronger evidence of which program interventions were most significant in reducing mortality. Additionally, highlighting improved antibiotic stewardship and conducting an economic evaluation of this program may demonstrate overall cost savings. These cost-savings may help justify the continuation of the CM-DTP and support this program becoming standard protocol for other institutions caring for CM patients. The results of this evaluation will be disseminated to those who make decisions about the procurement of supplies for CM treatment and diagnosis. The findings will also highlight the comprehensive benefits of this program to obtain continued hospital support for the CM-DTP.

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CHAPTER 3: Patient and Family Member Experiences of a Cryptococcal Meningitis Program in Rural Uganda: A Mixed Methods Evaluation of Barriers and Gaps

ABSTRACT

Introduction: Cryptococcal meningitis (CM) is attributed to 15% of all AIDS deaths. Research has focused on ideal treatment and diagnostics for this disease, yet little is known about the patient's experience with CM and what leads them to seek care. We explored the barriers and facilitators of patients and family members of deceased patients who participated in a CM Diagnosis and Treatment Program (CM-DTP) at Lira Regional Referral Hospital (LRRH) in Uganda.

Methods: A convergent mixed-methods study design was used to collect, analyze, interpret qualitative and quantitative data concurrently, and assess supporting or contradicting responses. Participants were 20 CM patients and 20 family members of deceased CM patients admitted to LRRH from February 2017-November 2019. Surveys were followed by semi-structured interviews. All interviews were audiotaped, transcribed, and thematically coded for analysis.

Results: CM understanding was lacking; only 17.5% of patients and family members knew all the complications of CM, while 10% and 40% respectively reported not knowing the cause of CM. Seventy percent of patients who died sought care three times or more compared to 35% of those who survived. The common barriers to CM care were related to a) lack of formal CM education, b) lack of CM understanding, c) stigma, d) delays in CM diagnosis and treatment, and e) mental health conditions such as depression and anxiety. The key facilitators for CM care were support from family, friends, other patients, and medical staff and having hope and purpose in life.

Conclusion: Patients are presenting to lower-level health facilities multiple times before being diagnosed and treated for CM. Additionally, there is a lack of patient education; patients reported their lack of understanding about CM and requested comprehensive education. Lastly, mental health screenings should be conducted to assess for issues with stigma and mental illness conditions.

Keywords: Cryptococcal meningitis, HIV patients, family members, mixed methods, rural Uganda

INTRODUCTION

In sub-Saharan Africa, the most common cause of secondary immunodeficiency is HIV/AIDS.[2] Since the advent of antiretroviral medications and expanded availability of these life-saving drugs, HIV death and morbidity has been reduced. However, challenges of antiretroviral therapy (ART) treatment failure in the form of drug resistance or non-adherence[3] can lead to opportunistic infections (OIs) which contribute to HIV/AIDS related death.[4] Currently, common OIs such as tuberculosis (TB) and fungal diseases, such as cryptococcal meningitis (CM),[5] are also common killers of people with HIV/AIDS.[6] Cryptococcal meningitis (CM) is a disease which causes infection of the brain and affects 220,000 people worldwide.[7] Each year, CM disease kills 181,000 people.[8] Research has been conducted to determine the most effective treatment combinations and medical therapies to improve mortality and morbidity.[9-16] However, there is a dearth of research to understand why CM is still occurring in the era of accessible ART. Immunosuppression due to ART treatment failure or non-adherence is well-established,[17,18] but the factors that contribute to the incidence of CM in this population are unknown.

High mortality among CM patients has been attributed to delays in care,[19-25] specifically delays related to ART initiation and care-seeking for CM diagnosis and treatment.[20-22] Potential reasons for CM-related delays were limited resources for treatment, diagnostic testing, and limited staff training in complex medical management.[19,26] These clinical factors are important to know; however, the psychosocial, spiritual, behavioral and cultural components related to barriers and facilitator to CM treatment and care remain unknown and are important to investigate.

In 2017, prior to the CM-DTP initiation, a needs assessment revealed that the basic supplies for diagnostics and treatments to implement Uganda's protocols for CM care were lacking. When supplies were unavailable, diagnosis and treatment costs were passed down to patients. If they were unable to afford diagnosis or treatment, outcomes became dire because without treatment, this disease is fatal.[27] After this assessment was conducted, the CM-DTP began at Lira Regional Referral Hospital (LRRH) to provide supplemental supplies, treatment and staff support for CM patients to improve CM diagnosis and care to decrease mortality and morbidity in the same year. This program was guided by the recommendations of Uganda Clinical Guidelines, which were developed by the Uganda Ministry of Health.

The CM-DTP was evaluated after two years of implementation showing an overall decrease in mortality, increase in diagnosis for CM, decrease in antibiotics prescriptions, and an increase of number of LPs performed. Additionally, patients had CM symptoms for an average of three weeks (20.7 days) before they received a definite diagnosis of CM, and 34% sought treatment prior to admission to LRRH (See Chapter 2). This finding demonstrates that delays in CM treatment exist; however, patients sought treatment from other primary clinics or hospitals prior to LRRH admission.

Currently, little is known about patients and family members perceptions during their experience with CM and the CM-DTP, and no studies to our knowledge have assessed family member's experiences. One study recounted a patient's experience with CM and found that the patient did not have an understanding of the disease or the necessity of long-term treatment with antifungal medications.[28] Although researchers recommended patient and public education related to HIV disease and treatment,[28-30] there is minimal evidence of education focused on CM or other OIs. Awareness of CM, and the disease's symptoms can improve outcomes, if knowledge, recognition of symptoms, and other factors of behavior change motivate a patient to seek care sooner. A timely evaluation can enable healthcare providers to deliver prompt diagnosis and treatment.

In summary, current literature supports the hypothesis that there are gaps in CM education and treatment and delays in diagnosis and treatment. Additionally, barriers in other determinants of health impede mortality outcomes for patients living in rural settings.

METHODS

Study Design

A convergent mixed methods design was used to collect qualitative and quantitative data concurrently. The patient and family member surveys were conducted and immediately followed by semi-structured interviews. This design was used to assess supporting or contradicting responses between qualitative and quantitative data. Semi-structured interviews allowed for probing after the survey to provide a more robust understanding of the survey responses through the incorporation of the participant's contextual perspective and experience.[33]

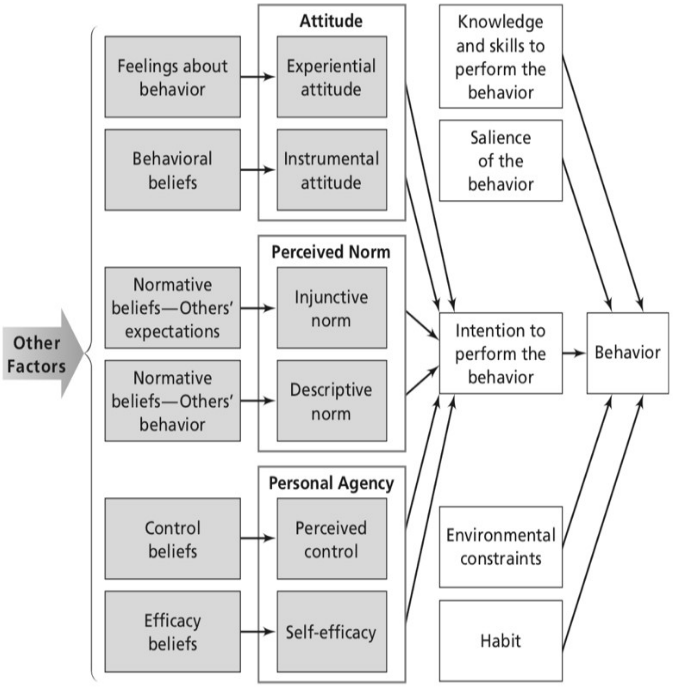


Figure 3.1. Integrated Behavioral Model (IBM)

Theoretical Model

The IBM guided the surveys and qualitative interviews and was the theoretical model used in this study. The IBM is an extension of the Theory of Reasoned Action and the Theory of Planned Behavior.[31] In addition to the key constructs of attitude, perceived norms, and personal agency, this model includes other factors related to the environment, habit, knowledge, and salience of behavior, which can influence behavioral intention[32] (Figure 3.1). In the qualitative interviews, we identified each key construct and factor related to the behavior of seeking medical care. The interviews provided deeper understanding of theoretical constructs that may affect care-seeking behavior. More information about the IBM can be found in Chapter 1. This study utilized the constructs from this model to formulate questions for the surveys and semi-structured interviews. Incorporating this model into our study produced a greater understanding of the gaps and drivers for behaviors related to care-seeking and treatment in patients.

Ethics Approval

Regional ethics approval by Gulu University Research Ethics Committee (GUREC), national ethics approval from Uganda National Council of Science and Technology (UNCST) and approval from the University of Washington Institutional Review Board were obtained to conduct interviews with patients and family members who were a part of the CM program.

Setting

Figure 3.2. Map of Uganda[1]

LRRH is a rural hospital located in northern Uganda, a region which was historically unstable due to the Lord's Resistance Army (LRA) rebel occupation for approximately two decades (from 1987 to 2006).[34] This instability led to poor healthcare infrastructure and resources in the region, including care and treatment for CM. Since this time, the region has grown to a catchment area of 2.2 million people. It is only one of two referral hospitals in this northern region of Uganda,[35] with the next closest referral hospital being located 63 miles away.

Sample

Patient Interviews/Survey: Twenty patients, aged ≥13, who were able to provide consent or obtain assent and participated in the CM-DTP at LRRH between February 2017-February 2019, were purposively sampled based on available contact information and received outpatient CM care; however, due to post-hospital deaths and inaccurate contact information, our sample size was not obtained during this time period. Our criteria for admission date was extended to November 2019 and after February 2019, and we invited patients prospectively as they were admitted until our sample size was reached. Patients were approached at follow-up appointments or invited by telephone to participate in the surveys and interviews. Phone numbers were identified through hospital records or clinical record forms.

Family Member Interview/Survey: Twenty family members of deceased CM patients who were a part of the CM-DTP at LRRH during the CM-DTP study period (February 2017-February 2019), aged ≥ 18 and knowledgeable about the patient, were purposively sampled based on their attending to the patient during the hospitalization and available contact information. However, due to limited and inaccurate contact information, our initial sample size was not obtained, and the date was extended to November 2019. After February 2019, family members were invited on a rolling basis until our sample size was reached. If patients in the sample died after discharge from their hospitalization and a family member who was an attendant was available, they were also invited to participate. Family members were invited by telephone to participate in the surveys and interviews and were asked about their knowledge of the patient's experience to assess their suitability to participate in the study. Phone numbers were located through patient records or clinical record forms.

Instruments

Surveys***:*** Patients and family members were asked about their knowledge of CM, experience with the CM program and personal attitudes of stigma among people living with HIV based on questions from the Uganda Demographic Household Survey (UDHS) and Uganda AIDS Indicator Survey (UAIS). Patients were also asked about their demographic information, ART history, health-seeking activities, and other questions related to the constructs of health behaviors as outlined by the IBM theory (Appendix A). Family members were asked about the patient's demographic information, ART history, behavior towards CM symptoms, care behavior, and treatments sought (Appendix B).

Semi-Structured Interviews: Patients and family members were asked questions about their experience with CM care at LRRH and their recommendations to improve the CM-DTP. Patient interviews sought to understand their issues around care-seeking and explored the constructs of intentions, attitudes, social norms, perceived control, critical events, alternative strategies, environmental constraints, and salience of behavior (Appendix D). Family member interviews attempted to understand the patient's experience of seeking healthcare for CM symptoms, as well as their social norms, environmental constraints, salience of behavior, perceived control surrounding care seeking, and CM and HIV treatment (Appendix E).

Procedure

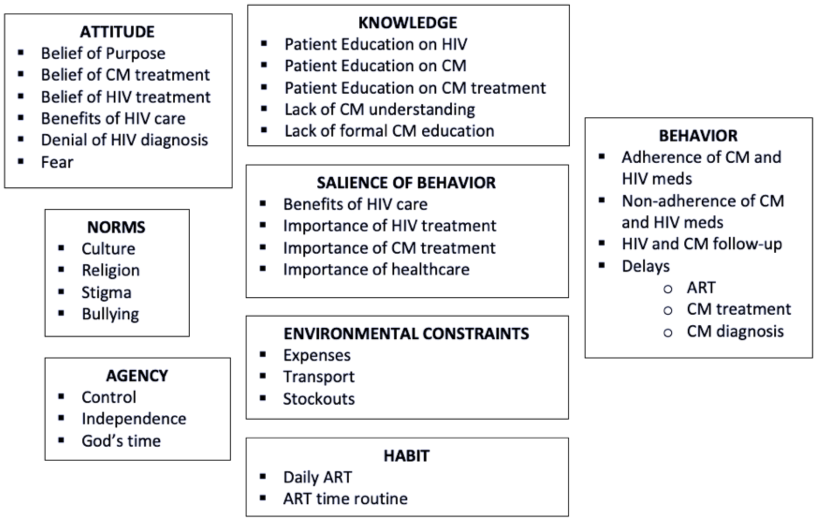
Surveys were proctored by trained interviewers in Lango or English for all patients or family members and conducted at LRRH. The surveys were completed prior to the interview on an electronic tablet using REDCap (Research Electronic Data Capture), which is a secure, HIPPA compliant, web-based application that is used for creating and managing online surveys and databases.[36] Trained interview staff conducted the semi-structured interviews in the participants' preferred language. Interviewers were also encouraged to probe participants further during the course of the interview to gain greater understanding of their perspective and experience. The interviews were audio recorded, transcribed, and then translated into English if translation was required in preparation for analysis. To verify the validity of the translation, audits of the transcriptions with the recordings were assessed by each transcriptionist.

Analysis

Surveys: Descriptive statistics, using means and proportions, were used to analyze the responses from the surveys regarding demographic information and barriers to care-seeking behavior, diagnosis and treatment. Questions in the survey were constructed using the IBM framework to assess which constructs of the framework were most commonly utilized for patients and family members related to behavior change. Additionally, questions related to stigma were descriptively compared to the responses from the UDHS survey and the UAIS.[37,38]

Transcripts: English language transcripts were entered into ATLAS.ti.[39] Initial coding and memo writing was performed by the PI, with the IBM framework guiding initial codes in the data. From these codes, networks and memos were created to generate further codes and establish major

Figure 3.3. IBM Framework for Patient and Family Member Coding



themes related to patient behavior towards adherence, non-adherence, and delays in care and treatment for HIV and CM. A primary code book was established to provide continuity in coding between the PI and one additional coder. Additional codes were added based on participants responses. All coded interviews were reviewed by the PI to ensure accuracy and continuity and to minimize discrepancies in coding between transcripts.

RESULTS

The following results highlights the findings from the surveys and interviews with patients and family members who participated in the CM-DTP. This information provided new insights and also confirmed findings from other studies. Results of the surveys are presented first, followed by interview findings and quotes from the participants.

Table 3.1. Demographic Information Results

DEMOGRAPHIC INFORMATION	**EXPIRED PATIENT**	**PATIENT**
AGE (mean, range)	34.9, 13-60	39.3, 17-63
SEX: Female (N (%))	10 (50%)	6 (30%)
Marital Status: Married (N (%))	10 (50%)	10 (50%)
Employment status	**(N (%))**	**(N (%))**
Full time	7 (35%)	7 (35%)
Part-time	0	3 (15%)
Seasonal	3 (15%)	2 (10%)
Unemployed	10 (50%)	8 (40%)
Education		
Post-secondary	3 (15%)	4 (20%)
Secondary	4 (20%)	4 (20%)
Primary	12 (60%)	9, 45%)
None	1 (5%)	1 (5%)
Healthcare facility for routine care		
Health Center II	0	1 (5%)
Health Center III	8 (50%)	8 (40%)
Health Center IV	6 (30%)	5 (25%)
LRRH	4 (20%)	5 (25%)
Average Monthly Income (mean, range)	162,233.3 (100-520,000)	186,803.2 (10,000-639,108)

Surveys

A total of 40 patients and family member were enrolled in this study which found that the average ages of those who died and lived were 34.9 and 39.3 years, respectively, revealing that those who died were slightly younger overall (Table 3.1). The two groups had similar education statuses, with 30-40% having completed secondary education or higher. Marital status was the same between the groups, and those who survived had a higher average monthly income compared to those who died at ($49.50 vs. $42.99, using a conversion rate of 3,700 Uganda shillings to 1 U.S. dollar).

CM Knowledge

Overall, less than half the patients and family members had heard of CM prior to their diagnosis (35%), and fewer patients than family members knew that it was recurrent (20% vs. 50%; Table 3.2). Fifty percent of family members and 45% of patients believed that HIV could be spread by saliva (Table 3.6). Only 10% of patients and 40% of family members knew that CM was caused by a fungus, while 17.5% of patients and family members knew all the complications of CM. During the course of the interviews, some family members mentioned that they had other family members or friends who had this same disease in the past. This may have been why some family members had more knowledge about this disease compared to patients.

Table 3.2. Knowledge Survey Results

KNOWLEDGE	**FAMILY MEMBER (N (%))**	**PATIENT (N (%))**
Heard of CM Prior to Diagnosis:		
Yes	7 (35%)	7 (35%)
CM can be recurrent		
Yes	10 (50%)	4 (20%)
CM Cause		
Fungus	8 (40%)	2 (10%)
Bacteria, Virus, or Tuberculosis	8 (40%)	12 (60%)
Unknown	4 (20%)	6 (30%)
CM Complications		
Vision loss	5 (25%)	5 (25%)
Hearing loss	1 (5%)	0
Death	8 (40%)	7 (35%)
All the above	3 (15%)	4 (20%)
I don't know	3 (15%)	4 (20%)

CM Experience

The most common symptom patients experienced was headache (90%), followed by fever and neck pain (Table 3.3). The majority of patients self-medicated (85%) prior to coming to LRRH for the primary purpose of pain relief (55%). Most patients (97.5%) received treatment at a health facility prior to their admission to LRRH, and the average waiting period from the time of symptom onset to see a health provider was 163 days for patients who died and 15.4 days for patients who survived. Among those who died, 70% sought care ≥3 times, while of those

Table 3.3. Health-Seeking Behavior Results

HEALTH-SEEKING BEHAVIOR	Expired Patient (N (%))	Patient (N (%))
Treatment sought at other health facility		
Yes	19 (95%)	20 (100%)
Type of health facility		
Clinic/Health Center II	3 (15%)	7 (35%)
Health Center III	8 (40%)	7 (35%)
Hospital/Health Center IV	7 (35%)	4 (20%)
LRRH	2 (10%)	4 (20%)
Times seen at other health facility prior to LRRH		
None (directly to LRRH)	1 (5%)	1 (5%)
1	2 (10%)	7 (35%)
2	2 (10%)	5 (25%)
3	2 (10%)	4 (20%)
≥4	12 (60%)	3 (15%)
Reason for health care treatment		
Worsening symptoms or no improvement	16 (80%)	70 (14%)
Referred	2 (10%)	2 (10%)
Seeking meds	2 (10%)	3 (15%)
HIV meds	1 (5%)	2 (10%)
Diagnosis at health facility		
Malaria	7 (35%)	8 (40%)
HIV	6 (30%)	2 (10%)
Typhoid	4 (20%)	0
Meningitis	0	2 (10%)
CM	2 (10%)	1 (5%)
Days waited until treatment sought	(Mean, Range)	(Mean, Range)
Days	163, 2-1095	15.4, 1-60

Table 3.4. CM Experience Survey Results

LRRH EXPERIENCE	Family Member (N (%))	Patient (N (%))
Best part of LRRH CM care		
Good care	18 (90%)	10 (50%)
Free medication	12 (60%)	12 (60%)
Life/ being alive	0	2 (10%)
Education	0	1 (5%)
Worst part of LRRH CM care		
Rude staff	5 (25%)	2 (10%)
Out of stock supplies	4 (20%)	2 (10%)
Paying for medications	2 (10%)	1 (5%)
Rude patients	2 (10%)	2 (10%)
Nothing	5 (25%)	9 (45%)

who survived, 35% sought care ≥3. What participants appreciated most about their stay at LRRH was the good care they received (70%), followed by the free medications they received (60%; Table 3.4). When asked about what they liked least about their hospital stay, the most common response was that there was nothing they were unsatisfied with during their stay (35%); however, some mentioned they had issues with rude staff (17.5%).

ART Experience

All participants were positive for HIV; however, 90% of those who died started ART while 80% of those who lived started ART (Table 3.5). Among deceased patients, 45% had stopped ART at one point, while 35% of those living had stopped ART. Of those who stopped

ART, the major reasons why they stopped ART were lack of support to continue their ART (25%), side effects (20%), and pill fatigue (15%). However, 94.4% of those who lived restarted ART, and all patients who died were on ART at the time of death.

Table 3.5. ART Experience Results

ART EXPERIENCE	Expired Patient (N (%))	Patient (N (%))
ART Started		
Yes	18 (90%)	16 (80%)
No	2 (10%)	4 (20%)
ART Stopped		
Yes	9 (45%)	7 (35%)
No	7 (35%)	9 (45%)
Reason for stopping ART		
Thought they were healed	2 (10%)	0
Unsupportive environment	2 (10%)	3 (15%)
Tired of taking	3 (15%)	0
Side effects	1 (5%)	3 (15%)
Restarted on ART		
Yes	9 (100%)	6 (30%)
On ART before death/discharge		
Yes	14 (70%)	19 (95%)
No	3 (15%)	0
I don't know	3 (15%)	0

Stigma

Several questions obtained from the 2016 UDHS and 2011 UAIS were used to assess the level of stigma participants experienced in the study. The answers were compared with the results from the national surveys. Questions about whether participants would buy food from a vendor with HIV and if children with HIV should be allowed at school with other children without HIV were indicator questions related to discrimination from the 2016 UDHS.[40] The results from our survey found that patients and family members had less overall discrimination compared to those who participated in the household survey from the same region. Ninety-five percent of study participants said they would buy vegetables from a vendor with HIV, compared to 86.2% from the household survey, while 97.5% believed children with HIV should be able to go to school with other non-HIV positive children compared to 83.9% in the household survey (Table 3.6). Additionally, the first three stigma questions were taken from the 2011 UAIS.

Overall, study participants had less stigma than those who participated in the AIDS survey. Study participants were more willing to care for a family member with HIV (97.5% vs.

94.7%) and believed that teachers with HIV should be able to teach in schools (90% vs. 79.9%). The question which had the largest perceived stigma results asked whether a family member's HIV status should remain a secret and found that 42.5% of the study participants wanted it to be a secret, compared to 34.2% from the national survey. Patients indicated that they would be ashamed if someone in their family had HIV (2, 10%) and they would want a family members' HIV status to remain a secret (7, 35%). These questions when asked to someone with HIV are indicators of self-stigma.

Table 3.6. Stigma Survey Results

STIGMA	Family Member (N (%))	Patient (N (%))
Would want a family member's HIV status to remain a secret*		
Yes	10 (50%)	7 (35%)
No	5 (25%)	12 (60%)
Willing to care for a family with HIV in their home*		
Yes	20 (100%)	19 (95%)
Would you buy vegetables from a vender with HIV?†		
Yes	18 (90%)	20 (100%)
Should kids be allowed to go to school with other kids with HIV? †		
Yes	20 (100%)	19 (95%)
People hesitate to take an HIV test because of fear of how others will react if test is positive†		
Yes	17 (85%)	19 (95%)
I don't know	2 (10%)	1 (5%)
People with HIV lose respect of other people†		
Yes	14 (70%)	15 (75%)
No	6 (30%)	5 (20%)
People talk badly about people with HIV†		
Yes	16 (80%)	18 (90%)
No	4 (20%)	2 (10%)
Fear that you can get HIV through saliva†		
Yes	10 (50%)	9 (45%)
No	9 (45%)	9 (45%)
I don't know	1 (5%)	2 (10%)
I would be ashamed if someone in my family had HIV		
Agree	2 (20%)	2 (20%)
Disagree	18 (90%)	18 (90%)

*Uganda AIDS Indicator Survey, 2011

† Uganda Household Survey, 2016

Interviews

Through the interviews with patient and family members, several barriers and facilitators of CM care were identified among those who were a part of the CM-DTP. Key barriers included: a) lack of formal CM education, b) lack of CM understanding, c) access to ART and HIV care, d) delays, e) mental health conditions, f) stigma and shame, and g) culture. Common facilitators to CM care were: a) CM understanding, b) access to HIV clinics and ART medication, c) habit, d) CM care, e) support, and f) purpose. Lastly, key reasons of delays for CM care were related to self-medication, multiple health center visits, misdiagnosis,

Table 3.7. Interview Code Results

CODES	**DEFINITIONS**	**PATIENT (N (%))**	**DECEASED PATIENT (N (%))**
Barriers to CM Care			
Lack of formal CM education	Had no formal CM education by healthcare providers about CM topics such as cause, symptoms, prevention, diagnosis, treatments, and side-effects	15 (75%)	15 (75%) (Family member)
Lack of CM understanding	Had incomplete understanding on CM cause, prevention, diagnosis, treatments, treatment duration, symptoms, or long-term effects	20 (100%)	20 (100%) (Family Member)
ART and HIV care	Lacked available of ART and HIV services	17 (85%)	18 (90%)
CM treatment and care	Experienced barriers to availability or affordability of CM treatment and care	7 (35%)	8 (40%)
Lack of support	Lacked encouragement from friends, family, or healthcare staff	8 (40%)	13 (65%)
Mental health conditions	Acknowledged mental health issues of depression or anxiety	5 (25%)	7 (35%)
Stigma/Shame	Experienced stigma related to HIV diagnosis and associated feelings of shame	7 (35%)	18 (90%)
Culture	Reported cultural beliefs of witchcraft and religious beliefs of prayers and faith healing	4 (20%)	7 (35%)
Facilitators to CM Care			
CM understanding	Understood some component of CM cause, prevention, diagnosis, treatments, treatment duration, symptoms, long-term effects	10 (50%)	13 (65%) (Family Member)
Access to HIV clinics and ART	Acknowledged facilitators of physical access or available transport to HIV clinics and available ART medication	20 (100%)	18 (90%)
Habit	Established a routine for administration and timing of ART	15 (75%)	5 (25%)
CM care (diagnostic and treatment)	Reported access to available and affordable diagnostics and treatments for CM care	12 (60%)	17 (25)
Support	Acknowledged encouragement and support from family, friends, and healthcare providers	19 (95%)	20 (100%)
Purpose	Experienced feelings of purpose or having something or someone to living for	3 (15%)	4 (20%)
CM Experience			
CM care delays	Experienced delays to CM diagnosis or care related to self-medication, multiple health center visits, misdiagnosis, culture/religion or personal beliefs	16 (80%)	18 (90%)

culture/religion, or personal beliefs. A comprehensive list of codes, their definitions, and the frequency of occurrence can be found in Table 3.7, followed by details of the themes and exemplar quotes.

Barriers

There were several barriers to CM diagnosis, treatment, and care that were revealed by the interviews. The key areas surrounding these barriers included CM education and knowledge, ART access, CM care and support, mental health conditions, stigma, and culture.

Lack of Education

All patients and family members reported some education related to HIV, but not everyone stated they had education about CM. From the surveys, the majority of patients (65%, n=16) had never heard of CM prior to their diagnosis. The amount and quality of education given to patients and family members varied. Twenty-three participants (57.5%) were able to discuss some aspect of the cause, symptoms, transmission, or prevention measures for CM accurately, while others had no knowledge of these topics. Exemplars from participants indicating that they did not receive education related to CM prevention or treatment included, "What are the prevention measures [for CM]?" and "…uh there is no knowledge [about CM], I was just told to take drugs [CM medications] well" indicated that patients and family members did not receive education related to CM prevention or treatment. Overall, a feeling of compliance to take medications because "they were told to" was expressed among a quarter of the patients, but they did not understand why they were taking the medications. The following statement also reinforced the lack of education provided to patients during their admission with the disease.

> I am not doing anything except for [taking] the medication they are giving me because they have not yet even taught me… you will do this to prevent that cryptococcal meningitis from coming back, they have not yet told me. (Patient, male, age 48)

Complications

Complications due to the disease and treatment were not uncommon for patients with CM. Patients had misconceptions of these complications, which can also become long-term disabilities such as cognitive impairments and hearing and/or vision loss. Statements such as, "It's because it [the medicine] made [me blind]" and "When he had just started, he was not blind, so we thought maybe the drip [IV medication] they [gave] him, either [the] water [normal saline] and drugs [CM medication] they could have given him [too much or] even if he ate [too] much," supported these findings. Statements such as these also confirmed the lack of education provided to patients and their family members.

CM Understanding

CM understanding was identified as the information patients were able to recall and verbalize when asked questions about CM. Many participants did not know the cause (75%) or transmission (50%) of the disease. Overall, the level of understanding of CM was higher among family members, who had more correct responses to the knowledge questions from the survey than patients (n=21 vs. 10). This may be attributed to family members being older or having past experience with CM through other friends and family members. The most common areas of knowledge gap were related to 1) CM disease, in general, 2) transmission, 3) treatment for CM, 4) prevention measures, and 4) early detection and treatment. The following statements reinforced a lack of understanding about CM:

> I only want to understand it, and if it is coming, how does it begin? And if it is healing, what damage does it leave on a person? (Patient, male, age 17)

> I am going to ask it again: Can it be transmitted through sex even? ...So, to prevent it, I must protect myself, by using like condoms. (Patient, male, age 23)

ART and HIV Care

In addition to lack of education and knowledge, barriers surrounding ART and HIV care can contribute to CM acquisition, as lack of access, not taking ART, or treatment failure can lead to lowered immunity. Some of these barriers stemmed from forces beyond their control, such as unavailability of drugs, lack of finances, and distance of the clinic from their home. However, barriers created through personal lifestyle choices, denial or disengagement, and diet were also disclosed. For example, some patients shared the following:

> Taking it [ART] would be difficult for me if it's like those days when I was taking alcohol. If you have already taken alcohol when you are going home, you tend to forget because you have already taken alcohol. (Patient, male, age 48)

> I kept on like that with my stubbornness, sometimes drinking, smoking, outings, intercourse but then things came to fall apart… (Patient, male, age 33)

Patients also delayed ART treatment for years citing that they did not feel ill and therefore did not need medicines. Most of these patients were on Septrin during this time period; however, only when they began feeling sick did they get retested and initiate ART.

> I was not sick. There was no knowledge. I was not sick at all. OK, after I became sick, and they confirmed it, I was like, oh, that was real. (after testing positive 3 years earlier; Patient, male, age 48)

> There was nothing like any pain; there was no pain in my body. I was just very healthy, and I just stayed like that. (16-year delay; Patient, female, age 50)

Participants emphasized the importance of having available food to take with ART. If ART is taken on an empty stomach, patients experienced untoward side effects like dizziness or nausea, which contributed to non-adherence of ART. Lack of finances contributed to their ability to buy appropriate food, and if it was not available, they would miss their dose until they were able to have a proper meal.

> If he was eating something that could make taking his medicine easy, [because] if you are satisfied, you can have the chance to take your medicine well without even fearing [the] medicine. (Family member of 27-year-old male patient)

> What makes taking medicine difficult, I said, it's food. Food that you have to eat, so if you're not eating, it reaches a time when [the] medicine will start rejecting you because it depends on what kind of food you are eating or you have to eat good food and then the medicine will accept you. (Patient, male, age 17)

CM Treatment and Care

The most common barriers to CM treatment and care were finances, inadequate laboratory testing, lack of treatment, and insufficient medical facilities to care for CM patients. Having patients visit health facilities with inadequate supplies not only incurred unexpected expenses for patients but also delayed their diagnosis and treatment for CM.

> Sometimes it's difficult because if you don't have money, and you say that let me go to the clinic, the person from there will ask you [for] money. And when the main hospital is too far, you also need boda [hired motorcycle transport]. And when the money is not there, you can even lose [your] life. (Patient, female, age 33)

> …the challenge was our laboratory or the laboratory of the hospital…everything we took there, they were saying they can't do… so it became a challenge because at that time, we didn't have…money. (Family member of 40-year old female patient)

Mental Health

Depression is a common mental health disorder among people with HIV; however, access for care is lacking due to few trained providers in mental health care. Even though there are still issues of stigma related to this topic, some patients and family members were open to talking about it. The terms depression and anxiety were not frequently used; however, euphemisms like "thinking too much" or "overthinking" were more commonly expressed. For those who had issues with depression or anxiety, it primarily affected their ability to take medications on a daily basis. For others, these issues led to feelings of hopelessness and more dire consequences which contributed to their death.

> She would agree to take the drugs, only that it was the fun makers [people making fun of her] that made her to overthink and she died. (Family member of 48-year old female patient)

> I have understood that this Cryptococcus meningitis is not a good disease; it disturbs a person so much and sometimes it can kill within a short while…because [this] time [I] felt a lot of headache. I lost hope of life in my heart. (Patient, male, age 26)

Stigma and Shame

Stigma related to HIV diagnosis is still a common experience in Uganda, and among the participants, half said they experienced stigma (51.3%). Additionally, the survey found that of those who died, 75% reported that they experienced stigma compared to the 27.3% who reported experiences with stigma and survived. These results reinforce the important role stigma plays not only in HIV care, but in the health cascade of people living with HIV and the potential for opportunistic infections like CM. This was also evidenced by these comments made by family members who lost their loved ones:

> …big people like her parents even said some things that would break her heart. They didn't give her what she wanted, and this created even more stigma. Then she became so angry, and she just thought that it is better to die. (Family member of 35-year old female patient)

> …she had that stigma which was killing her sincerely! (Family member of 40-year old female patient)

For those who experienced stigma, three key challenges were faced. The most frequent issues were feeling shame and/or fear, as well as being bullied. These feelings can come from many sources but, in this study, stigma was the primary source of these feelings. Participants particularly felt shame about their HIV status and were fearful of having others laugh at them or finding out about their status. These feelings typically affected their ability to go to the clinic or take ARVs, and for some, contributed to their death. The following responses from patients and family members reflect how shame and fear directly impacted the patient's lives and their ability to seek treatment for HIV:

Shame prevented patients from taking ART

> If you find receiving ART difficult, it means you are afraid; you are ashamed of yourself, and you have the fear that people will talk about your condition. So, because [of] this, you will find it very difficult, and you won't receive you[r] drugs. (Patient, male, age 40)
>
> He would feel a lot of shame that people would laugh at him, that this person is on ARV. That['s] what people in the village fear… (Family member of 60-year old male patient)

Fear of being seen collecting HIV medications

> …she would fear that people would laugh at her, and people would talk that this person is sick, [and] saw him/her getting the drugs. That is what brings fear. (Family member of 48-year old female patient)
>
> I think it could be fear because whatever brings shame start(s) with fear… but for him, he was fearing. (Family member of 37-year old male patient)

Bullying by community members

Another common manifestation of stigma was people bullying or making fun of patients based solely on their HIV status. These experiences scarred them emotionally, leading some to feel hopeless:

> …she fears because she would say that people laugh at people if you have the HIV virus. They laugh at people, and they like bullying them. They like bullying people." (Family member of 32-year old female patient)
>
> Sometimes, they can just say that, 'You people who are having HIV, you're just wasting your time. You can die any, any day and any time. You're not supposed to even stay with us because you are now hopeless.' (Patient, female, age 33)

Cultural Factors Contribute to CM Care

In Uganda, a strong sense of cultural or traditional beliefs is held and practiced, which may conflict with information from a Westernized medical lens. The following are some of the conflicts patients had while making decisions about their health and medical care.

Traditional healers and witch doctors

> It was his brother who brought in the idea of visiting a witch doctor to find out why the headache is too much, but the patient refused the idea and said he will just go to the hospital. (Family member of 56-year old male patient)

> …a sister of mine there told me that it's possible someone has bewitched you, so they should first take me to someone there to see. And, yet, that person was a real witch doctor. And then I said, 'Let me just die, if I can die.' And then I refused. I refused. It was of benefit [because] if I had gone there, I would have been dead already… (Patient, male, age 48)

Religious beliefs

Religion also plays an important part of Ugandans' lives and beliefs about healing through prayer or rituals can dissuade patients from continuing medication and other treatments in hopes of a cure for HIV and other illnesses. The following quotes demonstrate this:

> …she started telling me "I went to TB Joshua [pastor in Nigeria] to pray for me…" so and I told her that "You my sister. You are not taking your medication right," and she kept quiet…so after going to Nigeria, she came back. That is when she told me that… "They told me to stop taking drugs [ART]." (Family member of 40-year old female patient)

> …does HIV get cured? Because I have heard some people, some pastors, say that [through] praye[r], it can get cured. (Family member of 31-year old male patient)

Facilitators

There were several facilitators that participants indicated helped them receive appropriate care for CM and ART. The key areas were knowledge about CM, access to ART, and support for ART adherence, including emotional support.

CM Understanding

Participants were able to describe some of the symptoms they encountered with CM, as well as the consequences of what happened when they did not take their ART. The understandings they obtained about CM and the disease process were primarily through their own personal experience with CM, either as a patient or a family member attending to a patient. They were aware of the severity of this disease and the importance of early diagnosis and treatment in saving one's life. For example, as it relates to how CM is transmitted, one family member had this to say:

> That disease [CM], I think it is not transmitted sexually; I think it's transmitted through air. That is how I thought about it. But as someone who was attending to him, I used to be so close to him, but I didn't get it. But I know I don't have any knowledge concerning it because, for me, I thought cryptococcal meningitis is spread through the air… (Family member of 27-year old male patient)

For those who knew about CM symptoms, knowledge was acquired primarily through the experiences patients and family members had with this disease. The following statements demonstrate some of the problems patients experienced during the course of their illness:

> What I know from CM are the signs and symptoms that manifest with pain in the neck that cannot even allow you to turn around, and [the pain] also attack[s] you from the back. (Family member of 41-year old female patient)

> Cryptococcal meningitis can make someone deaf because she also, when she was getting the other drug, sometimes she said she couldn't hear. And they sen[t] her to the outpatient there to see the doctor. And the eyes – sometimes she says she [can't] see far. (Family member of 39-year old female patient)

Patients and family members knew that fluconazole was a common medication for CM, and they understood that taking medication (e.g., ART and fluconazole) was a key factor in preventing and treating CM, as evidenced here by these patients:

> I didn't take my medicine [ART] well by the time I was entering 2018. Taking my medicine was not good, and then [I acquired an] opportunistic infection. (Patient, male, age 35)

> What I can only do is to continue [the] medication. And I need to eat energy-giving foods and frequently visit the hospital to do [the] viral load test so that I can know how it is because when the viral load is high, it reduces your strength. But when the viral load is low, it can fight against all kinds of viruses in you. (Patient, female, age 55)

Access

For participants, the availability of medicines; access to nearby health facilities, diagnostics, and transportation; and financial resources encompassed the key factors for accessibility of quality healthcare. From the participants' statements, access affected multiple aspects of their life, including their ability to receive ART and obtain HIV and CM care. In this study, access was defined as a construct of environmental constraint based on the IBM theoretical model.

ART. Access to an ART clinic is a major facilitator for ART adherence. The experience at the ART clinics was important for most participants. Of particular importance was receiving timely ART distribution, decreasing pill burden, and living near a clinic or having easy access to transportation to visit a clinic. These were all facilitators for ART procurement and important factors for ART adherence, as conveyed here by the following quotes:

> I came and I was given the [HIV] drugs and went back with it. It was easy because the drug was available. If not, it was going to be difficult. (Patient, female, age 50)
>
> Yeah, the distance from the… hospital was not that far. (Family member of 29-year old female patient)

Habit

Another important facilitator for ART adherence was expressed by patients who integrated pill-taking into their daily routine, resulting in habit-forming behaviors. Participants shared the following:

> He had good eating habit and he would take his medicine after brushing. (Family member of 60-year old male patient)
>
> Taking it daily – it's not easy. But now with time, I continue taking it. Then I [got] used to [it] because… I have been given advice to take it well. (Patient, male, age 23)

Support

Most participants felt that they had some form of support or were a source of support for their family member during their experience with HIV and CM. Those who did have support reported positive experiences with HIV care and felt encouraged. In contrast, those who did not have support were more likely to self-isolate and suffer from other mental health conditions, such as depression and anxiety. Having positive experiences at the ART clinic through relationship building with health workers and patients and other sources of support helped facilitate consistent HIV care for patients.

> He found it easy because he kept seeing his other friends going to get their HIV meds, and this motivated him. And I also kept telling him that the meds will make him stay alive and keep his children, hmm. His friends and the health workers kept encouraging him to feel free. (Family member of 56-year old male patient)

> [Healthcare staff said] that I should not fear taking the medicine, since they were giving me the medicine. If I stopped taking it, I would die. They told me with a good heart and not with harassment. Then I started using the medicine by that time very well… (Patient, male, age 35)

Additionally, having visits from friends and family provided encouragement and gave them a sense of belonging and renewed focus for life, as demonstrated by these comments:

> Some of his relatives would visit him and his friends. So, I just tell them, if the patient is there, it's not good *not* to visit, so people were visiting him. They could encourage him. (Family member of 29-year old male patient)

> I got it easy because I kept seeing from my friends. So, I just decided that if you are taking the drugs, that is what makes you healthy. You don't get any problem so long as you['re] adhering well to your drugs as instructed…I'm just taking it that way, and that's why I'm still alive till now. (Patient, female, age 42)

Support was also found within in the forms of hope and a sense of purpose. This provided patients internal encouragement for a better life, not only for themselves but also for their families:

> He had the hope that he would get better. (Family member of 16-year old male patient)…my kids are supposed to be in [my] future. I have to think then…I'm supposed to be alive. Then these kids of mine [can] study [go to school]. I should fight for my life, then they [can] also [have an] easy life. (Patient, female, age 33)

Cryptococcal Meningitis Experience

CM Care Delay

The initial symptoms of CM present similarly to more common diseases such as typhoid or malaria. Ninety percent of family members and 80% of patients shared that they had delayed CM care, which was related to self-medication, multiple health center visits, misdiagnosis, culture/religion, or personal beliefs. The following statements are some of the reasons for delays related to patients believing that their symptoms were mild enough to treat at home and self-medicate:

> The reason why she took long without treatment [is] because she was taking painkiller[s] that would sometimes make her feel better. (Family member of 41-year old female patient)

> In October, it happened. It was like as if it was malaria. Then I kept taking traditional medicine, and then it disappeared. Then in November, I went somewhere. And I came back….it started [again in] November last year. (Patient, male, age 35)

In addition to self-medicating, others also went to multiple health centers for diagnosis and treatment, which delayed CM diagnosis and treatment. This family member shared their experience:

> We moved in different health centers like Otuke health center, Abongomola health center III so, when we saw no improvement, [we] then decided to come here in the main hospital (LRRH). (Family member of 29-year old male patient)

Other reasons for delays were due to expenses related to transport: "It [the hospital] is a little bit far… and money [is not there]…" Additionally, some patients believed that they were strong and healthy enough to overcome this disease on their own, while others were fearful of going to the hospital:

> …[He] was convinced that even when he does not take the medicine, he will not die [because he was blood type O]. [Then] it reached a point when was weak and, when we talked to him, he at last understood… (Family member of 60-year old male patient)

> I think she was afraid [to come to the hospital]. Then this thing [CM] came very serious[ly] just at once. (Family member of 48-year old female patient)

DISCUSSION

To our knowledge, this study is the first of its kind, obtaining crucial information from patients and family members through interviews and surveys about their experiences with CM. One case study described a patient returning with CM complications after being diagnosed three months earlier, but information about their experience with CM care was not explored.[28] No studies were identified that have evaluated this population utilizing mixed methods while exploring diagnosis, care, treatment, and their journey with CM. Centering the experiences of patients and family members provided novel information and revealed five key themes which affect patients and family members experiences with CM: education, stigma, delays, mental health, and support.

Education

The findings illustrated that patients and family members had little understanding of and received little education about CM. Many participants did not know that CM was caused by a fungus or that it could reoccur if not treated properly. Moreover, the majority of patients did not know that maintenance therapy for CM could last for years, depending on their CD4 count. It is clear from the findings that more education is needed for CM in every aspect. This education must provide comprehensive information on the cause of CM, as well as its transmission, diagnosis, treatment, and prevention. The authors from one case study stated," [the patient] was not aware of the cause, treatment options, and duration and the need for long-term/life-long suppression therapy for [their] condition."[28] That finding was similar to what participants shared in this study.

There are also topics related to HIV that need to be readdressed during HIV counseling and follow-up. Specifically, information focusing on the way HIV is and is not transmitted should be continually reinforced. Approximately 50% of the participants believed that HIV can be transmitted through saliva, a common misbelief that has been difficult to dispel. There is an evident lack of information regarding the basic facts of CM, and much of this information could be distributed through CM awareness campaigns via T.V., radio, or newspapers. Disseminating information in these ways would provide a rapid and efficient means to circulate it quickly and reach the larger community.

Stigma

Stigma is one of the main factors contributing to ART adherence since ARVs became available.[43] From the responses in this study, it is clear that stigma continues to play a profound role in people's lives, especially for those with HIV. Stigma not only factors into one's ability to take and maintain the drugs that will save their life, but it also plays a significant role in their ability to live life and feel that they have purpose. The majority of participants who died (75%) had previous experiences and personal impacts related to stigma, compared to participants who are still living (27.3%). Although no studies have indicated a direct causal link between stigma and mortality, it is a moderator which affects people's ability to get tested for HIV,[44,45] adhere to ART[43] and engage in HIV care.[44] Many participants who faced stigma had feelings of fear and shame associated with their HIV status, which were fostered during their interactions with their community, family and friends. They acknowledged that this fear and shame contributed significantly to their ability to take their medications and to seek treatment for HIV. In conclusion, the effects of stigma continue to be a major barrier to HIV care and play a major role in CM acquisition.

Delays

There were many factors reported to have contributed to delays in seeking CM care. One factor was lack of knowledge of CM symptoms which prevented patients from seeking care quickly and led many to self-medicate prior to seeking medical treatment. This is consistent with findings from the UNHS regarding care-seeking behavior, which showed that the majority of people (57%) did not seek healthcare because they thought the illness was not severe enough for medical consultation.[37] Additionally, nearly all of the participants had sought healthcare prior to LRRH admission and were seen multiple times at other health facilities. This supports the finding that some delays can be attributed to lack of knowledge at the health provider level and/or lack of diagnostics available at lower-level health centers in turn contributing to misdiagnosis. Missed opportunities to diagnose, treat, and/or refer patients on their first visit create delays in CM care, increase the severity of this disease, and makes it more difficult to treat, which leads to poor patient outcomes. This study found that participants who sought care multiple times at other health facilities had higher mortality compared to those who sought care fewer times. One study in the U.S found errors in diagnosis in 5% of patients who sought care in an outpatient setting.[46] Applying this error percentage to the current Ugandan population of 42.7 million[47] would account for approximately 2.1 million errors per year. However, these errors are projected to be higher in lower to middle income countries due to limited resources related for diagnostics, fewer trained staff or specialists, and access to electronic medical record keeping.[48] A review of diagnostic errors reported that misdiagnosis can come from common conditions (like malaria), as well as rarer illnesses[49] such as CM. The most common diagnoses patients had from other health facilities before coming to LRRH were malaria (37.5%) and HIV (20%). Delays to appropriate care through referrals can also contribute to delays in diagnosis, which can have dire consequences for patients with CM. Understanding the root causes for these errors is necessary to ensure improvements in accurate and timely diagnosis and treatment for the care of CM patients.

Other factors that contributed to delays were cultural factors, specifically religion, traditional beliefs, or witchcraft. Some patients delayed treatment in exchange for seeking traditional treatments, while others turned to their religious beliefs and relied on prayers for healing. Some patients stopped all their medications, including ARVs, due to the belief that they would be healed. The CM-DTP study found that 9% of participants sought traditional medicines and 5% sought religious healers or witchdoctors prior to being diagnosed with CM (Chapter 2). Researchers also concluded that the average time from symptom onset to hospitalization was two weeks. This finding was similar to the results in the analysis of the CM-DTP at 16.4-22.3 days (Chapter 2) and patient's report of symptoms days from the survey, which averaged 15 days.

Mental Health

Mental health is a common but misunderstood condition in Uganda and plays a role in CM care. Treatments for mental health conditions such as depression and anxiety are not commonly given due to limited mental health service availability in Uganda.[50,51] Mental health is still an unrecognized condition for many Ugandans,[52,53] even though the prevalence of serious mental illness in people living with HIV ranges from 11.05-17.4% in Uganda.[54,55] However, some participants acknowledged that depression played a role in their ability to seek HIV and CM care. From the interviews, two main factors were associated with mental health: the first being stigma and the ramifications that stigma brings and the second being support (or lack thereof). According to the findings in the UAIS, "stigma leads to secrecy and denial that hinder people from seeking counselling and testing for HIV, as well as care and support services."[38] Stigma is a common predictor of mental illness among people living with HIV, and one study found that 7.9% of the participants who were depressed had experienced AIDS-related stigma.[54] A meta-analysis explored the association of HIV-related stigma and health outcomes and found that stigma was associated with lower social support and increased anxiety and mental distress,[56] which was also reported by the patients and family members during the interviews. This study also found that patients who had more support from family and friends appeared to have fewer issues with mental health conditions, compared to those who had less support or had strained relationships in their life. This finding was also supported by another study conducted in Uganda.[57] Little research has been conducted on mental health conditions related to CM among those living with HIV, but it certainly plays a role in the relationship between ARV adherence and overall patient health, which is important to understand when assessing patients and their ability to maintain their health and take the treatments needed for CM and HIV. Further investigations should explore the effects of CM on mental health.

Support

The findings of this study detailed the barriers patients and family members faced while navigating their care with CM. Much of what they shared illuminated the difficulties they encountered with this disease. However, support was a key facilitator in CM care. Some participants had to be physically supported to come into the hospital, as they were so weakened by the disease or were sometimes unconscious. Relying on family and friends, for some, is what saved their life. Support from family, friends, other patients, and medical staff were all key contributors to participants' sense of purpose and well-being. Studies have also shown that the positive effects of social support in the form of support groups, peer groups, and counseling for people living with HIV improve adherence to ART and linkage to HIV care.[57-59] Having people encouraging them to seek treatment and take their ART and providing positive experiences gave them hope, motivation, and belief in a future. Our findings show that support—physical, emotional, and spiritual—is an important component in providing hope and encouragement. As such, its importance should not be overlooked.

Limitations

There are important limitations to note in this study. First, participants were identified through phone calls, which excluded potential participants who did not have a recorded contact number, access, or the financial means to afford a phone. This limitation may have excluded participants who were more representative of the population. Secondly, the sampling strategy may have introduced recall bias, as some of these participants, specifically those who were treated for CM two to three years ago, may not have accurately recalled specific details, such as dates and treatments compared to participants who were seen within the past few months. Family members likely had a harder time recalling certain details compared to patients. For example, family members reported 163 mean symptoms days versus 15.4 days among patients, which could suggest recall bias on the part of the family members. To mitigate this limitation, when lapses in memory existed or conflicting information was given, this data was classified as unknown or was cross-checked with clinical record forms which were collected during the time of the participant's admission to validate information such as admit dates and symptom days.

CONCLUSION

We found evidence that patients were self-medicating, which may have prolonged the time from symptom onset to presentation to health centers. Patients sought care at lower-level health facilities (primarily HC II and III) and returned to these facilities multiple times before they were properly diagnosed and treated for CM. We also found that the majority of patients were not given sufficient information about CM and were unaware of the cause, transmission, symptoms, or the importance of timely and continued treatment for this deadly disease. Lastly, mental health issues and stigma are not routinely assessed among patients with HIV or CM, leaving many of these patients untreated which can contribute to poor health outcomes and developing OIs like CM.

We recommend CM awareness campaigns for the general public and continuing medical education for healthcare providers on CM cause, symptoms, diagnosis, and treatment. This education for providers should prioritize those working at HIV clinics and those who practice at lower level health centers, as these sites are typically the first point of contact for patients to receive CM diagnosis, treatment, or referral. Education for providers should focus on the updated Ugandan guidelines for CM diagnosis and treatment. This education will equip providers with the ability to identify CM earlier and educate all patients and family members. The focus of patient and family member education should include basic facts about CM– specifically the cause, symptoms, transmission, and treatments for this disease.

Lastly, we cannot ignore the significance of mental health conditions and stigma on ART adherence. Education should be given to healthcare providers and counselors to have all HIV patients screened for depression and counseled about basic mental health illnesses, as well as if they should be referred to a counselor or a mental health provider for further evaluation and/or medication intervention. Incorporating these recommendations will bring us closer to providing holistic CM care with the ultimate goal of renewing hope and saving lives.

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CHAPTER 4: “If you don’t know… you cannot suspect what you don’t know”: Barriers and Facilitators of Cryptococcal Meningitis Care for Healthcare Providers in Rural Uganda

ABSTRACT

Introduction: Cryptococcal meningitis (CM) is one of the deadliest opportunistic infections related to HIV/AIDS. Extensive work surrounding CM has focused on effective medication and treatment combinations, yet the barriers and facilitators of CM diagnosis and treatment from the perspective of healthcare providers at primary care facilities are not fully known. To improve CM diagnosis, treatment, and care, understanding the barriers and facilitators of health providers encounter when providing CM care is essential.

Methods: A convergent mixed-methods study was used to collect qualitative and quantitative data concurrently at the top 10 referring sites for CM patients to Lira Regional Referral Hospital (LRRH) in Uganda from February 2017-February 2019. From each site, two healthcare providers were selected by the in-charge supervisor and were invited to participate. Twenty providers were surveyed and interviewed. Interviews were recorded, transcribed, and thematically coded for analysis.

Results: Approximately half (55%, n=11) of the providers knew how CM was transmitted, and 75% (n=15) were aware of its cause. Only 15% (n=3) knew the duration of CM maintenance therapy, and most providers (74%) last had CM education during their professional schooling. One quarter (25%) disclosed that they never give education about CM to their patients; the reasons were due to time constraints (30%) and lack of knowledge (30%).

Conclusion: Providers reported that having available diagnostic and treatments for CM would improve timely care for patients. Also, CM education is needed for providers and for providers to pass on this learning to their patients regarding CM cause, transmission, and treatment. Providers believe they are responsible for providing patient education and requested continuing medical education for themselves. An education curriculum for CM should be developed for both healthcare providers and patients in collaboration with the Ministry of Health.

Keywords: Cryptococcal meningitis, healthcare providers, mixed methods, education, rural Uganda

INTRODUCTION

Cryptococcal meningitis (CM) is a disease which affects 220,000 people worldwide and kills 181,000 people annually.[2] Most of the current research on CM focuses on determining the best medication combinations and treatment therapies to improve mortality and morbidity. However, little research has been done with the people at the front line of service: the healthcare providers. There is a lack of information about the barriers and facilitators providers face when caring for patients with CM. Understanding their experiences will provide crucial information on what service gaps exist and how to improve CM care at the local health facility, which is the patient's first point of entry.

Current treatment guidelines for CM include: Cryptococcal antigen (CrAg) testing, combination therapy with fluconazole, IV Ampho B or flucytosine, IV hydration, therapeutic lumbar punctures (LPs), routine blood testing, and supplemental electrolytes.[3] To implement these guidelines, the government should provide CrAg testing kits and antifungal medications for CM treatment; however, in practice, supplies are often out of stock and treatment and costs are passed down to the patient. How frequently supplies are out of stock and what happens when patients cannot afford these costs in rural areas are unknown. Current studies support ongoing education for health providers, and studies confirm that CM education is being conducted.[4-7] However, the level of knowledge and frequency of CM education, and whether or not this is occurring in rural areas, is unknown for both providers and patients.

Background

In 2017, a needs assessment at LRRH revealed that the basic supplies and medication to implement Uganda's protocols for CM treatment were lacking. It was observed that when supplies were out of stock or unavailable, the costs of diagnostics and treatment were passed onto patients and family members.[8] If they were unable to afford these costs, they were clinically diagnosed with CM, treated with suboptimal therapy using fluconazole monotherapy,[9-11] or delayed treatment until they were able to afford antifungal medications.[8] In response to these findings, a CM Diagnosis and Treatment Program (CM-DTP) began in order to improve CM care and decrease mortality and morbidity based on Uganda's guidelines. This program provided supplemental supplies, treatment, and staff support for CM patients at LRRH. A recent analysis of this program found that 34.1% of the patients were referred from surrounding health facilities (Chapter 2). It is evident that patients are seeking care outside of LRRH, and a mixed-methods study with CM patients found that treatment was sought ≥3 times at lower health facilities among 70% of the patients (Chapter 3). This finding supported provider-side delays related to CM diagnosis, treatment, or referral to LRRH.

Additionally, these delays introduce questions related to misdiagnosis or missed diagnosis. Data from the patient study showed that most patients were diagnosed with malaria (75%) at these health centers, while only 20% were diagnosed with CM or meningitis before arrival to LRRH (Chapter 3). This information creates confusion about whether these patients had confirmed malaria, were misdiagnosed, or had a co-infection with malaria. It is unknown whether malaria was confirmed in these patients at the health centers or if they were clinically diagnosed or treated empirically based on their symptomology.

Review of the literature found a case study that was conducted in rural Uganda of a patient who was seen for recurrent CM. At readmission, it was reported that "[the patient] was not aware of the cause, treatment options, and duration and the need for long-term/life-long suppression therapy for (their) condition."[12] This case illuminates the issue of whether or not patient education occurs for CM. If education is not provided, what are the barriers for patient education from the provider's perspective? The findings from the previous chapter verified that few patients and family members received education on CM, specifically its cause, symptoms, transmission, and treatment duration (Chapter 3). This study investigated the providers' practices around patient education on CM, as well as the barriers to education. It also inquired about the overall experiences providers had regarding their own CM education, examined general practices around diagnosis and treatment with CM patients, and explored who is responsible for providing education to patients.

In summary, current literature supports that there are gaps in patient and provider education on CM, delays in treatment due to the unavailability of supplies, patient-related delays, and other unknown gaps in providing care in rural settings. This study assessed these gaps through surveys and interviews among providers in rural Uganda to better understand and discover barriers and facilitators of CM care from the healthcare provider's perspective.

METHODS

Study Design

A convergent mixed methods design was used to collect qualitative and quantitative data. The surveys were conducted first, immediately followed by semi-structured interviews for each provider. Utilizing this design allowed for differences in responses which either supported or contradicted the responses between the qualitative and quantitative data collected.

Theoretical Framework

For this study, the Integrated Behavioral Model (IBM) was used as the theoretical framework which guided surveys and interview questions to assess the key constructs and factors that were considered when providers chose behaviors related to diagnosis, treatment, referral, education, and overall CM care. This behavioral model is an extension of the Theory of

Reasoned Action (TRA) and the Theory of Planned Behavior (TPB) and assumes that the best predictor of performing a behavior is linked to intention or motivation.[13] This model integrates additional factors of behavioral intention, such as the environment, habit, knowledge, and saliency of the behavior while incorporating the baseline theoretical constructs of attitude, perceived norms, and personal agency found in the TRA and TPB.[14]

Setting

Lira is located in the Lango subregion of rural northern Uganda, which is surrounded by nine districts.[8] These districts encompass several types of health facilities including district hospitals and clinics: health center (HC) II, III, IV, and private facilities. These facilities provide patient referrals to the regional referral hospital in Lira, Uganda, which is one of two referral hospitals in this northern region of Uganda[15] and serves approximately 2.2 million people.[8] These smaller surrounding clinics and hospitals provide patient referrals to LRRH because of limited resources or lack of specialists and equipment for diagnosis, treatment and care of CM.

Figure 4.1. Map of Uganda, NUMAT Program Districts[1]

Sample

Clinic Sites: Ten area HC III and IV sites (public and private), located within the nine districts, were selected for this study. These sites were chosen based on the number of CM patient referrals made to LRRH, obtained from clinical record forms (CRFs) and hospital record data between February 2017 and February 2019. The top 10 sites with the highest referrals were selected.

Providers: Two health providers aged ≥18, who diagnose and treat patients and were willing to participate in the study, were selected from each of the 10 health facility sites, leading to a sample total of 20 healthcare providers who were surveyed and interviewed. The two providers per health facility were selected by the supervising staff at each health facility to participate in the study.

Recruitment

The consents and surveys were completed prior to the interview on an electronic tablet using REDCap (Research Electronic Data Capture), which is a secure, HIPPA compliant, web-based application that is used for creating and managing online surveys and databases.[16]

Instruments

Surveys: Information obtained through the surveys pertained to the provider's demographics, as well as their knowledge of CM, HIV stigma, patient education, and current Ugandan guidelines for CM screening and treatment. These questions fell under the constructs of knowledge, attitude, and behavior from the IBM model. Stigma-related questions were acquired from the 2016 Uganda Demographic Household Survey (UDHS) and 2011 Uganda AIDS Indicator Survey (UAIS) and were used to address the attitudinal measures from the IBM theoretical model (Appendix C).

Semi-Structured Interviews: The interviews inquired about providers' experiences with CM patients. Specifically, providers were asked questions to assess patients' barriers and facilitators for CM diagnosis and treatment, their perspectives on CM patient education, and their recommendations to decrease barriers to improve CM outcomes and education. Interview questions also assessed their perspectives on issues surrounding diagnosis and treatment to better understand the behaviors, intentions, attitudes, social norms, perceived control, critical events, alternative strategies, environmental constraints, and salience of behavior. (Appendix F)

Procedure

The in-charges (supervisors) of each of the 10 health centers were contacted by telephone as a courtesy call to obtain verbal consent for access into their health facility before our arrival. Upon arrival, the in-charge selected two providers for study staff to approach. After explanations of the study were provided and consent obtained, REDCap surveys were completed on an electronic tablet and were proctored by trained interviewers in English if providers needed help with the survey platform. All documents were uploaded to the server at the end of each collection day.

Semi-structured interviews with interview guides followed the surveys, which were conducted in English and audio recorded. This format allowed interviewers to gain more in-depth information to corroborate and provide contextual meaning to the responses from the survey and interview questions. The recordings were transcribed in English by study staff and experienced transcribers. To verify the validity of the transcriptions, audits were conducted with each transcriber. Intermittent audits of the transcription were also conducted to ensure the quality and accuracy of the transcripts.

Ethics Approval

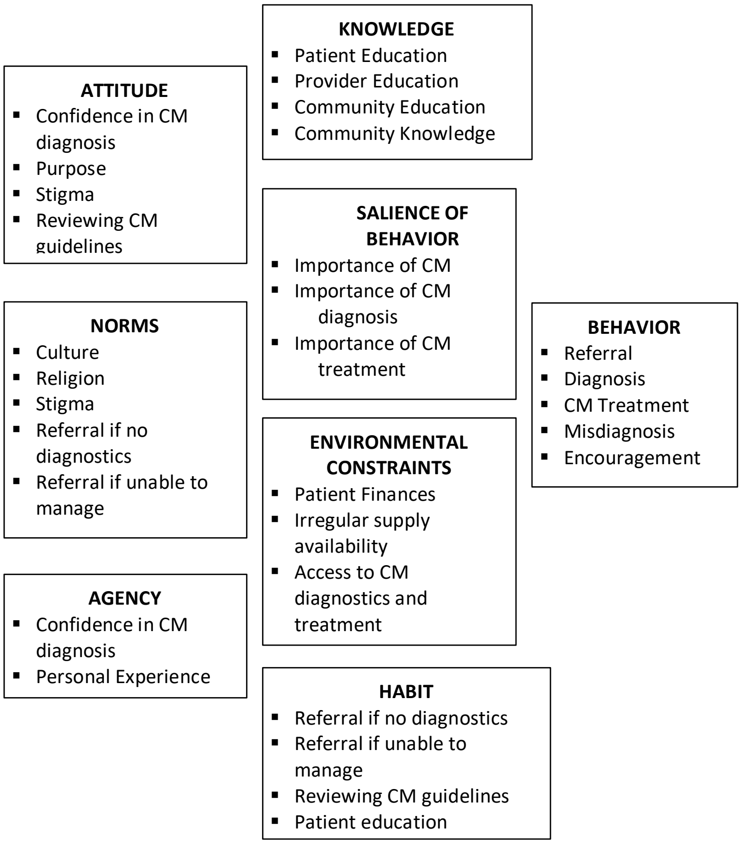
Regional ethics approval by Gulu University Research Ethics Committee (GUREC), national ethics approval from Uganda National Council of Science and Technology (UNCST), and approval from the University of Washington Institutional Review Board was obtained for conducting surveys and interviews with healthcare providers. Permission was also obtained from the Lira District Health Officer to enter the private and public health centers in Lira District.

Analysis

Surveys: Means and proportions were obtained using descriptive statistics, which analyzed responses from the surveys on demographic information and barriers to education, diagnosis, and treatment. Survey questions also assessed which constructs were utilized by providers when making decision about their behavior. Lastly, stigma questions were compared to the responses from UDHS and the UAIS and analyzed descriptively.[17,18]

Transcripts**:** ATLAS.ti was used to code transcripts.[19] Initial coding and memo writing was performed by the PI using the IBM framework to guide the development of the code book (Figure 4.2). Using these codes, networks and memos were created to generate additional codes, and major themes were extracted related to provider's behaviors and perceptions towards education, diagnosis, and treatment for CM. A primary code book provided continuity in coding between coders, and additional codes were added if new information was obtained from providers' responses. To ensure accuracy and

Figure 4.2. IBM Framework for Provider Coding



continuity and to minimize discrepancies of coding between the PI and one additional coder, all transcripts and codes were reviewed by the PI. Discrepancies were resolved by discussions with the PI and the additional coder to understand why the transcript excerpts were coded a specific way. After further clarification, codes were either changed or left in their original form.

RESULTS

The results from the provider surveys and interviews gave insight about their perceptions and experiences while evaluating, diagnosing, and treating patients with CM. Providers were candid about their experiences and shared recommendations to improve overall CM care. The survey results are presented first, followed by the interview findings.

Surveys

Provider demographics were majority male (60%) with an average age of 32.7 years (SD: ±8.2). The positions they held were medical officers (MOs; 25%), clinical officers (COs; 35%), nurses (35%), and midwives (5%; Table 4.1). The mean number of years of employment at their facility was 5.2 (SD: ±4.4). Half of the participants were employed in private facilities, and 40% of those working in private facilities were MOs.

Table 4.1. Provider Demographic Information Results

DEMOGRAPHIC INFORMATION	N= 20
Age (mean, SD)	32.7, ±8.2
Sex: Male (N (%))	12 (60%)
Employment status: full time (N (%))	19 (95%)
Years employed (mean, SD)	5.2, ±4.4
Provider Type	**(N (%))**
Medical Officers	5 (25%)
Clinical Officers	7 (35%)
Comprehensive Nurse	7 (35%)
Midwife	1 (5%)

CM Knowledge

Provider knowledge of CM: Approximately half of the providers *(*45%) did not know that CM was transmitted through the air, and 25% did not know that it was caused by a fungus

Table 4.2. Provider Knowledge Results

KNOWLEDGE	(N (%))
CM Cause	
Fungus	15 (75%)
Bacteria, Virus, or TB	5 (25%)
CM Transmission	
Airborne	11 (55%)
Blood, contact, sexual contact	9 (45%)
Who is susceptible to CM?	
Immunocompromised	20 (100%)
Length of CM maintenance treatment	
1 month	5 (25%)
6 months	9 (45%)
1 year	3 (15%)
CD4 ≥200	3 (15%)
Availability of Amphotericin B	
Not available	13 (65%)
Sometimes available	7 (35%)
What CD4 is used to screen for CM?	
<200	6 (30%)
Other	14 (70%)
What diagnostic tests do you use for CM?	
Lumbar Puncture or CSF analysis	9 (45%)
India Ink	4 (20%)
CrAg test	11 (55%)
CBC/Blood Culture	2 (10%)
I don't know	2 (10%)
What treatment do you give most often for CM?	
Ampho B	8 (40%)
Fluconazole	7 (35%)
Ampho B and fluconazole	5 (35%)
What do you need to diagnose CM more accurately?	
India Ink	5 (25%)
CSF/Lumbar Puncture	4 (20%)
CrAg Test	13 (15%)
CSF Culture	5 (25%)
Blood Culture	2 (10%)
X-ray	1 (5%)
I Don't know	1 (5%)

Table 4.3. Patient Knowledge and Education Results

PATIENT KNOWLEDGE AND EDUCATION	(N (%))
Do patients know about CM symptoms?	
Yes	2 (10%)
No	18 (90%)
How many patients heard about CM before their diagnosis?	
None	10 (50%)
Few	6 (30%)
Most know	2 (10%)
I don't know	2 (10%)
How often do you educate your patients about CM?	
Never	5 (25%)
Rarely/Sometimes	7 (35%)
Monthly	2 (10%)
Weekly	3 (15%)
Daily	3 (15%)
What prevents you from educating your patients?	
Lack of knowledge	6 (30%)
CM is not common	2 (10%)
Workload/lack of time	6 (30%)
Patients no show/missed appts	1 (5%)
Nothing	5 (25%)

(Table 4.2). The majority of those who did not know the basics of CM were nurses. Only 15% of the participants knew that the duration of CM maintenance lasted until the CD4 count reached ≥200. Of the three providers who knew about CM maintenance, two were MOs, and one was a CO. The current gold standard of CM diagnosis is CSF culture, followed by LFA (lateral flow assay) CrAg (cryptococcal antigen); however, 25% (n=5) of the providers believed that India ink, which has a sensitivity and specificity of 86.1% and 97.3% respectively, was the best way to diagnose CM.[20]

Patient knowledge of CM: The majority of providers (90%) did not believe that patients know the symptoms of CM, and half did not think that patients knew about CM before they acquired the disease (Table 4.3). Over half (60%) disclosed that they sometimes or never give education about CM to their patients, and the reasons given for this were time constraints (30%) and lack of knowledge (30%).

Recommendations

Providers were cognizant of their lack of education and knowledge about CM, and they recommended providing continuing medical education (CME) for staff and organizing CM education days for providers to improve education at their facility (Table 4.4). They also shared that they needed more treatment supplies and more time for patient education and testing in order to improve care for their patients.

Table 4.4. Provider Recommendations

RECOMMENDATIONS	**(N (%))**
Recommendations to improve CM education in the facility	
Trainings/Continuing medical education	11 (55%)
CIE materials	1 (5%)
Set Education days for pts	4 (20%)
Schedule workplan	2 (10%)
Increase patient time	1 (5%)
Pt keep time	2 (10%)
What is needed to provide better care to CM patients?	
Drugs/testing supplies	14 (70%)
Knowledge	11 (55%)
Community sensitization	2 (10%)

Stigma

Half of the stigma related questions in the survey were taken from the 2016 UDHS and the 2011 UAIS. Responses from the survey were compared with those from the national survey. Three questions from the UDHS were indicator questions related to discrimination. These questions specifically asked whether one would buy vegetables from a vendor with HIV and if teachers and students with HIV should be allowed to be in school with other students (Table 4.5). All the providers answered that they would buy food from vendors, and that students and teachers with HIV should be allowed to be in schools.

Lastly, more national survey participants would care for a family member with HIV in their home compared to providers (94.7% vs. 90%). Overall, providers had less stigma compared to other Ugandans, but they did still have issues with stigma, as 20% reported they would want their family member's HIV status to be a secret and would be ashamed if someone in their family had HIV.

Table 4.5. Provider Stigma Results

STIGMA		(N (%))
Would want family member's HIV status to remain a secret*		
	Yes	4 (20%)
	No	16 (80%)
Willing to care for a family with HIV in their home*		
	Yes	18 (90%)
	No	2 (100%)
Should teachers with HIV be allowed to teach in school? †		
	Yes	20 (100%)
Would you buy vegetables from a vendor with HIV? †		
	Yes	20 (100%)
Should kids be allowed to go to school with other kids with HIV? †		
	Yes	20 (100%)
People hesitate to take an HIV due to fear of how others will react if test is positive		
	Yes	18 (90%)
	No	2 (10%)
People with HIV lose respect of other people		
	Yes	8 (40%)
	No	12 (60%)
People talk badly about people with HIV		
	Yes	13 (65%)
	No	7 (35%)
Fear that you can get HIV through saliva		
	Yes	5 (25%)
	No	14 (70%)
	I don't know	1 (5%)
I would be ashamed if someone in my family had HIV		
	Agree	4 (20%)
	Disagree	16 (80%)

*Uganda AIDS Indicator Survey, 2011

† Uganda Household Survey, 2016

Interviews

The interviews with providers revealed key barriers and facilitators of CM care for providers and their patients. Common barriers were identified as: a) lack of CM knowledge, b) lack of CM education, and c) patient delays to care related to culture, religion, or lack of patient knowledge. Additionally, facilitators to CM care included: a) CM knowledge, b) patient education on the basic facts of CM, and c) support by healthcare providers and other healthcare workers. Table 4.6 provides a summary of key codes that emerged from the analysis of the provider interviews.

Table 4.6. Provider Interview Codes, Definition and Counts

CODES	DEFINITIONS	PROVIDER (N (%))
BARRIERS TO CM CARE		
Lack of CM education	Provider statements of lack of education or no further CM education outside of professional schooling	17 (65%)
Lack of CM knowledge	Self-report of incomplete knowledge of CM cause, prevention, diagnosis, treatments, treatment duration, symptoms, or long-term effects	17 (65%)
Delays	Patient delays to CM care due to culture, religion or lack of patient knowledge	9 (45%)
FACILITATORS TO CM CARE		
Continued CM Medical Education	Provider requests of education on CM cause, prevention, diagnosis, treatments, treatment duration, symptoms, long-term effects	20 (100%
Patient Education	Reports of needed patient education on CM cause, prevention, diagnosis, treatments, treatment duration, symptoms, long-term effects, and prompt care	20 (100%
Referrals	Patient referrals due to illness severity, lack of CM diagnostics, treatment, or lack of finances	20 (100%)
Support	Patient encouragement and support from healthcare providers and other healthcare staff	7 (35%)

Barriers

Providers cited several barriers for CM diagnosis and care for themselves and their patients. These barriers included lack of knowledge, education, and delays related to patients' cultural or religious beliefs. These factors were significant obstacles for providers in their pursuit to provide timely and accurate CM diagnosis and care to reduce CM mortality and morbidity.

CM Knowledge

Providers readily admitted to their lack of knowledge regarding CM and mentioned topics such as CM symptoms, diagnostics, and treatment about which they had little knowledge. This supported the survey findings, which showed that no one in our sample was able to answer all of the CM knowledge questions correctly. Without knowledge, providers reported that they cannot adequately treat or educate a patient with CM:

> I think I can say inadequate knowledge about cryptococcal meningitis. It can be the major barrier because if you don't know or if you cannot suspect what you don't know…if you don't have any knowledge about Cryptococcus just like anybody, you may not be able to even think of it or prevent [it]. (Clinical officer, M, 39)

Lack of CM Education

When talking about education, more providers spoke about the areas of education that were lacking. Most providers (75%) shared that they had had no CM training since medical or nursing school, which was over 15-20 years ago for some. A few providers (25%) did have some training within the last two years. Those who did have training were primarily MOs or COs. No nurses had recent training, as evidenced by the following statement:

> I have never been trained…in school – not specifically. The cryptococcal meningitis was only being mentioned as one of the infections of the brain, following immunosuppression or malnutrition, meaning when the immunity is weak, it gains access. (Nurse, M, age 30)

In 2016, an update of the Uganda clinical guidelines was distributed for healthcare providers on CM treatment. Most providers (70%) admitted that they had rarely or occasionally reviewed the national guidelines for CM screening and treatment. Those who did review the guidelines regularly were MOs or COs, who used them as a reference when needed.

> …guidelines are there, but if the client is before you and there is no suspicion, then reviewing it might take some other time. It is not always reviewed, once in a while, if you suspect. (Clinical officer, F, age 34)

> We always refer our self to clinical guideline. But, even in that clinical guideline, the knowledge is not as wide. (Nurse, F, age 30)

There were also some providers that stated they had never seen the guidelines. Those who admitted to this were primarily nurses and reported the following:

> That alone, I can’t deceive because I have never seen… have never reviewed it. (Nurse, F, age 27)
>
> I have never thought of it, reviewing…I have never thought about it, because this is [a] health center III, and the management of cryptococcal meningitis when it has reached the severe stage [of CM disease] … The services [are] not there. (Nurse, M, age 30)

The majority of the nurses in this study worked in HC III locations and rarely saw CM patients in practice. Due to the lack of diagnostics and treatment at their facility, they had less knowledge about CM and less experience. Typically, seriously ill patients that presented to their health center were transferred to higher-level facilities that had the capacity for diagnostics and treatment. The following statements provide justifications for why they did not review the clinical guidelines for treatment:

> I cannot say I am having much confiden[ce] in it because I have never managed the condition (CM disease). (Nurse, F, age 27)
>
> No, we just refer [if there are no supplies]. But our level here – health center IIII – we just refer for better management to health center IV or hospital. (Clinical officer, F, age 60)

Overall, providers admitted that they needed more education about CM, including its cause, mode of transmission, how to diagnose it, and how to treat it, especially in relation to the three stages of CM treatment and monitoring. Providers made the following comments:

> I would like to know, I would like to know, how is cryptococcal meningitis is [it] transmitted from one person to another: the mode of transmission? (Nurse, F, age 30)
>
> I have been challenged, I think, by that. I will have to read seriously (laughs) so that, so that I really get to know all about meningitis: the presenting signs, the key things that will make at least diagnosis [possible], even if am waiting for the confirmation from the lab. I should be having it on tips, on my fingertips, the key things that will make me diagnose that this is cryptococcal meningitis, the prompt treatment that should be given, and where not possible, where to refer… (Nurse, F, age 32)

Delays

The providers revealed that some delays were related to patients relying on traditional or religious beliefs, seeking care from witchdoctors, or soliciting prayers for healing and guidance. These conflicting beliefs of traditional and Western medicine must be taken into account when addressing issues with delays in care for many diseases, especially for CM where timely treatment is imperative. The following are exemplars of this conflict as providers relayed their experiences with patients:

> ... some people may think it's demon possession of the patient. So, they sometimes, they may prefer to go back [home]. At times, you may refer them to go, maybe, to go to other [health center] level. Then they will prefer to go back home to go and pray or to go to a witchdoctor because that— Those are some of the cultural beliefs of the community… (Clinical officer, M, age 31)
>
> Of course, sometimes, they bring late. And they're like, we're still praying. So, the community should also be knowing what it is about this disease and how does it present. (Nurse, F, age 32)

Based on the interviews, providers cited key barriers for CM diagnosis, treatment, and care. These barriers focused on the provider's lack of education and knowledge, as well as inadequate supplies and cultural or religious differences. Identification of these barriers provides awareness of these issues, which will help inform future interventions to mitigate these challenges in CM diagnosis and care.

Facilitators

Major themes related to facilitators included knowledge and education for patients, and provider support was also identified as a key factor for improving CM diagnosis and care.

CM Knowledge

All providers reported that knowledge in all diseases is an important aspect of their job and is relevant to every part of their job: assessments, diagnosis, treatment, and referrals. Ultimately, saving lives is the most important reason for this knowledge, especially for patients with CM. The providers were aware of the importance of knowledge and expressed their rationale for its importance throughout the interview process:

> First of all, you have to have the knowledge about it: how it presents, yeah. And then secondly, you have to have a good history from the patient, then [from] the tests, which are there. (Clinical officer F, age 27)
>
> It is important to know so that you can act appropriately. You refer in time or, if the drugs are there, you can give the right drug. (Clinical officer, F, age 60)

Most providers reported that it was important to diagnose patients correctly in order to provide correct treatment and to prevent untoward outcomes such as mortality and morbidity. Providers knew that in order to treat patients correctly and prevent death, they needed to ensure correct diagnosis:

> Diagnosing correctly would mean that treatment would be started. And in time and in the end, it will not only save the life of the patients but also the quality of life. (Clinical officer, M, age 39)
>
> The importance will be giving him or her better management. You'll give the treatment if you've already diagnose[d], give the right treatment because now if I misdiagnose you and give you another treatment then, …that one you will not get better…and your outcome will be poor. (Clinical officer, F, age 34)

Continued CM Education

Providers were cognizant and voiced the importance of education for themselves and for their patients. For example, one provider shared the following insight:

> Education is, I believe, that it's one of the best, approaches to healthcare because once somebody knows about what is happening to them or what is likely to happen to them, then they are capable of regulating or preventing themselves of getting into such a thing… and also by updating somebody with sufficient knowledge— They say that education is power; knowledge is power. Hmm, if you know it, then you can be able to do what is necessary to either avoid or to treat it, um, or to cooperate…(Medical officer, M, age 34)

Uganda has continuing education requirements for MOs, COs, and nurses; however, it does not specify what topics of education need to be reviewed. When asked what topics they needed most education on, topics of non-CM conditions were mentioned because of the frequency of their encounters with these diseases:

> …mostly it's non-communicable diseases that is hypertension, diabetes that are always neglected hence other diseases we always get...education on some of the opportunistic infection[s] in HIV. (Clinical officer, F, age 34)

Patient Education

All providers believed it was important to educate their patients on CM to improve their outcomes and to prevent CM from reoccurring. They also understood that education brings awareness of the disease and symptoms. It helps patients understand the importance of seeking care sooner, facilitating early diagnosis and completing their treatment to improve outcomes. These feelings were reflected in the following statements:

> …it is important to me because… health educating a patient— It will make that patient who is down there or who is having those signs to come up or come to the hospital and get treatment. And to me, it will be a great privilege to me in a way that I would have reduced [the] morbidity rate... (Nurse, F, age 30)

> …we need to come to a point of being able to regularly educate our patients, to be able to know the predisposing factor, causes, and maybe the mode of entry— The mode of infection of this organism. (Medical officer, M, age 34)

An important education topic that was frequently mentioned was for patients to know the importance of staying on their HIV medications to prevent opportunistic infections like CM. Providers had similar thoughts regarding what patients should know and provided the following suggestions:

> … we need to let them know that if they don't take medicines well, the viral load will rise. And the body system, for [the] immune system, will be compromised, and they will be at the risk of contracting cryptococcal meningitis. And then, also, we need to know about cryptococcal meningitis: how it presents and the outcomes of somebody who has cryptococcal meningitis… (Clinical officer, M, age 31)

Additionally, providers emphasized the importance of coming for evaluation quickly and not delaying care. They knew that the severity of the disease increased as patients waited longer to seek care or delayed diagnosis and treatment. Providers stated that they wanted to inform patients about the potential outcomes of this disease, hoping patients would seek treatment sooner when their symptoms first begin.

> …they should not take time before coming to this. They should not stay at home… going to any health center or where they can get any services…They themselves should, should have knowledge about the CM… (Nurse, M, age 22)

The facilitators for CM care were education and knowledge for providers and their patients. Education leads to knowledge, which helps providers pass on their knowledge to patients. Providers wanted to focus specifically on topics of basic CM facts, ART adherence, the seriousness of the disease, and not delaying care for patients, while recommended topics for themselves focused on general CM knowledge, diagnosis, treatment, and information about common diseases that they see frequently in their facility. They believed that through education, they can improve diagnosis and treatment for patients with CM and become better educators for their patients.

Referrals

Many of the facilities (70%) we conducted interviews from were HC IIIs, which have limited capacity for diagnosis and treatment for CM. They are referring sites to LRRH; it was reported that "severe cases" were typically referred to LRRH quickly. For some providers, they identified severe cases as those who had symptoms of loss of consciousness or confusion, or patients who were "not doing well." The following statements are how some providers justified their decision for referral of patients:

> When the patient is presenting with, OK, when the sign and symptoms [are] severe-- which we can't handle here — which needs those…tests to be done immediately.…When the results are needed soon, we refer it…If you're in severe cases, we refer. (Nurse, M, age 22)
>
> If the government fails and we have seen that this patient is presenting with the signs of cryptococcal meningitis, eh, we always refer them to main hospital because we know there it is a free service. And with the fluconazole, the price is very *high*. Other people they cannot afford, so we always end up referring them to the government hospital where they can get free service… (Nurse, F, age 30)

The lack of proper diagnostics and treatments or lack of patient funds provided the impetus for referral. All HC III facilities (n=7) referred patients rapidly when patients presented to their facility, while private and HC IVs attempted some diagnostics, as well as treatment, before referring to LRRH. The decision to refer also included the capacity for diagnosis and treatment available at their facility:

> …those things in our laboratory is too small. We need well-equipped lab which can do certain tests, verifying those… fluids. But also, we do not have …the lumbar puncture needles. We do not have it, so we can't even attempt. Um better to send away (refer patients to another facility) than keeping it longer. (Medical officer, M, age 35)
>
> …reagents are not there, OK. Um, always like for us, here, it can take five months without. And every time, they need to refer them somewhere. (Clinical officer, M, age 39)

Support

Stigma continues to play a central role in a patient's ability to seek healthcare, specifically related to HIV treatment. The providers were cognizant of this, recognized that they play a role in stigmatized attitudes, and stated how they can support and encourage patients to continue on their ART medications to maintain their health. The following statements were made by the providers:

> … stigma: if we…mistreat our clients, our clients will leave their drugs. And once they leave their drugs, their immunity is, ah, compromised and then they develop CCM [cryptococcal meningitis], so we need to really have a good association with, ah, with the clients so that, ah, they don't miss their dosages. They come for their treatment, and they will have a better life. And, ah, they will not develop CCM because we have seen people who develop CCM… (Medical officer, M, age 34)

> …we should do what we feel that we are doing our best because by giving them support by just talking to them – uh, encouraging them – telling them what to do when they on medication and giving them the right medicine in the right time and at the right place. (Clinical officer, M, age 25)

Recommendations

The key recommendations to improve CM care focused on education for providers so they can, in turn, educate their patients and to provide good services to their patients. Providers shared that implementing these interventions would improve overall care for their patients and provide encouragement for them to engage in care and improve their health outcomes.

Provider Education

Providers recommended having CME courses be made available to them on the topics of CM and HIV that would provide them with the most current information and recommendations for diagnosis and treatment. This education platform is familiar, as they are required to take CME courses as a condition for their license to practice. Having up-to-date information on CM will also provide better care for their patients:

> …we have to always update ourselves about the new guidelines and the general knowledge about what cryptococcal meningitis is and the outcome it is within the communities. (Clinical officer, M, age 25)

> Health workers should have the knowledge about cryptococcal meningitis so that he is capable of passing the information to the patients and to educate the communities. Health workers should also know where to manage and how to manage cryptococcal meningitis. (Nurse, M, age 30)

Patient Education

The topic of patient education is a recurring theme in this study and was cited again by providers as a recommended intervention to prevent CM and improve patient outcomes:

> …the best management is preventing the advanced diseases. So, as a health provider, we should also be keen so that if we can diagnose this illness earlier on when these people are at least still moving, can still eat, can still maybe get all treatment, it's best. So, we have to be keen mostly when we are dealing with people at risk of cryptococcal meningitis. We should always ask signs and symptoms that suggest they are heading to and give appropriate treatment and also give health education to the community so that when they have seen— Of course, some of them, you will still carry to the pastors thinking that it's demonic, so we should also give that health education. (Nurse, F, age 32)

Quality Care

Providers believed that quality service included correct diagnosis, access to diagnostics and treatment, and providing patient education. Some providers also mentioned the importance of respectful care and support through encouragement and education. Services and support encompassed quality care, as evidenced by the following quote:

> By giving good services itself to, to the patients…So services: I mean giving, actually assessing rights, then diagnosing well, and treating and giving the right information, giving health education about CM. (Nurse, M, age 22)

DISCUSSION

This is one of few studies conducted with healthcare providers assessing their experience with CM in rural Uganda. This study synthesized several key themes that were elucidated from the providers regarding their experience in diagnosis and care for patients with CM. The themes encompassed issues related to knowledge, education, delays, and quality care. Many of these themes were interwoven throughout the interviews and were recurrent among the providers.

Education and Knowledge

Providers

A key finding was the acknowledgement of providers' lack of knowledge and education on CM. The majority of the providers reported no past CM training beyond schooling and few had seen or reviewed the 2016 Uganda treatment guidelines for CM. MOs and COs were the only providers who had any training outside of school. Those who had the least amount of knowledge, experience, and training were nurses and midwives, even though they are usually the first point of contact for patients and constitute the majority of lower-level health center (HC II and III) workers in Uganda.[21] Additionally, 25% of providers still believed that India ink, which has a sensitivity of 86% compared to CrAg LFA at 99.5% sensitivity, is still the best way to confirm CM.[20] According to the WHO, the "lack of provider education and awareness about cryptococcal disease has also been identified as a cause of suboptimal management."[3] Similarly, lack of provider education and awareness was a major finding in our study and presented several times in many conversations with providers over the course of the interviews. Uganda has continuing professional development in the form of continuing education units (CEUs), which are required annually for doctors[22] and every three years for nurses.[23] A variety of activities are allowed to meet these requirements, including weekly staff meetings; however, CEUs do not require any specific medical education topics.[22,23] Providers expressed their lack of knowledge about CM and the minimal opportunities for continuing education; however, they did understand the importance of early detection and treatment for CM for positive outcomes and survival. Overall, the interviews revealed crucial gaps related to provider education and knowledge of CM, which dispelled any potential assumptions that healthcare workers are knowledgeable about CM.

Patient Education

The providers recognized not only their need for continuing education through CMUs, but also their responsibility to educate patients about CM. Providers stated which topics of education were needed for patients, including CM's cause, symptoms, prevention, and treatment. They also emphasized the importance of staying on antifungals and ART. However, if providers do not know basic CM facts, they cannot be expected to educate patients. Education must first be given to providers so that they can then pass it on to patients and make them aware of CM symptoms. In this way, they can increase the likelihood that patients will seek treatment at the health center more quickly, receive accurate diagnoses, and complete treatment. Providers reported that the greatest barriers for patient education were lack of time and knowledge (60%), which also need to be addressed by the facility. A study supported these findings, which found that staff shortage, limited opportunity for continuing education, and lack of time interfered with patient education.[24] Another study found that the culture of the organization or the facility impacted the motivation and value perception of patient education among nurses.[25] With the support of the health facility, providers can take steps to create a culture of education and make patient education a norm among providers, which will help facilitate this behavior in order to improve patient outcomes.

Delays

Providers perceived delays to be caused by a lack of available supplies and treatments, as well as patients lack of knowledge and cultural/religious conflicts. Past studies attributed poor outcomes for CM related to patient-side delays; however, in the previous study (Chapter 3) patients often sought care multiple times at health facilities prior to being diagnosed. Over 70% had gone to a health facility ≥3 times before their referral to LRRH and CM diagnosis (Chapter

3). This finding is more indicative of potential misdiagnosis or missed diagnosis by providers at the lower health facilities. Although no providers voiced any issues with misdiagnosis, they did mention the difficulties of diagnosing without proper testing and awareness of how CM presents. Diagnostic errors can lead to delayed care or even death among patients. The WHO published its findings on this topic and reported that the burden of these errors in primary care settings is higher in middle-to low-income countries specifically due to lack of diagnostic tests, fewer qualified healthcare providers, and paper-based charting.[26] This is concerning, as these lower-level health centers are where patients have their first encounters in seeking healthcare. The recommendations to remedy future errors can be accomplished through 1) improving education and skills, 2) empowering patients through education, 3) improving health systems, 4) enhancing access to health information technology, 5) increasing access to testing, and 6) learning from past errors.[26] These particular recommendations validate the need to educate healthcare providers in these lower health centers and the patients they serve. Providers were forthcoming about the difficulties in diagnosing CM due to similar patient presentation with more common diseases such as typhoid, malaria, and other forms of meningitis. They strongly recommended having diagnostic testing supplies available at their facilities to decrease the chances of misdiagnosis. Lack of supplies continues to be a barrier for diagnosing and treating CM at the lower health facilities and improving access to these diagnostics will help mitigate future errors in diagnosis.

Quality Care

Providers acknowledged that stigma is still a barrier to healthcare in patients with HIV. Furthermore, the results from the stigma survey showed that providers also have discriminatory attitudes towards people living with HIV. Although they have less stigma and discrimination compared to the general population in Uganda, these attitudes continue to be prevalent in the country. Providers expressed the important role they play in providing medical care, education, and support for these patients. They believe that the support they provide will help encourage patients to stay on their medications for HIV and CM. The study of CM patients supports this perception, as they confirmed that provider support and encouragement helped with their retention of ART (Chapter 3). Other studies verified the importance of support through social groups, family members, counselors, and respectful patient/provider relationships for people living with HIV/AIDS.[27-29] Providers are important to patients' lives and should be aware that they play not only the role of healer but also those of educator and supporter.

Limitations

Our clinical sites were chosen based on the number of CM referrals made to LRRH. This may have introduced selection bias, since not all health centers surrounding the hospital had an equal chance of being selected and were representative of all the health center patients seek care from. All facilities selected were either HC III or IV sites; no HC II sites were selected as they did not meet the criteria of being one of top 10 referring sites. However, HC II facilities have even fewer resources, and we may have found similar barriers in care related to supplies, education, and knowledge.

Participants were selected by the in-charge supervisor at each clinic site. The supervisors were more aware of the provider's work schedule and the staff that were available to participate in the study; therefore, they preferred to choose the provider participants. However, this sampling method may have diminished the representativeness of healthcare providers in rural Uganda. Additionally, some interviewer bias was present; it was found that as more interviews were conducted, participants had increasingly similar answers to the open-ended questions. Among participants who were interviewed toward the end of the data collection period, more closed-ended or leading questions were asked based on the responses from past participants, rather than open-ended questions, which may have led to more biased responses.

CONCLUSION

Key findings were: 1) there was a lack of knowledge of CM for both providers and patients which may have a direct impact in delays to care, diagnosis, and treatment; 2) to improve knowledge, education needs to be provided for providers on CM to improve outcomes and for providers to pass this knowledge to their patients; 3) supplies are lacking in the health facilities for diagnosis and treatment, leading many health centers to refer to LRRH due to patient's financial constraints or lack of diagnostics and treatment for CM at lower-level health centers; and 4) provider support is a facilitator for patients to continue their ARV and CM mediation. This support provides patients with encouragement and helps reduce feelings of experiencing stigma and discrimination from medical staff, which improves patient-provider relationships and patient health.

Recommendations

Healthcare providers recognized the need for continuing medical education on CM for all levels of healthcare facilities. However, as the lower-level health centers serve the greater rural population, and providers in these health centers had the least CM knowledge, education should first focus on these providers. Education can be given through a formal in-service training program and through CMEs provided by local professional boards or through the regional referral hospital. Additionally, providers should be educated on how to provide quality patient care, which includes information on supporting and educating patients, as well as the effects of HIV stigma and implicit biases that may hinder patient adherence to medications and treatments. An education curriculum developed for patient and provider education can incorporate comprehensive information about HIV, CM, and other OIs to increase their knowledge of these topics. Both curriculums should be developed at the government level to maintain continuity and consistency in verbiage and content around CM information and education. This requires the collaboration and assistance of the Uganda Ministry of Health to standardize protocols and curriculums regarding HIV and CM training and education for providers and patients. We plan to share these findings with each of the health facilities who participated in this study– LRRH staff and administration and Ministry of Health officials– to collaborate in the creation of a standardized education curriculum on CM.

Additionally, providing basic diagnostic tests for CM to all HC III and IV facilities in the form of LFA CrAg strips can expedite accurate diagnosis of CM when patients first arrive, instead of delaying their care until the third or fourth visit. Lastly, CM screening of HIV patients should be implemented to prevent fulminating CM and to treat latent fungal infections before they become life-threatening. Through the implementation of these recommendations, we aim to increase access for CM care and improve knowledge for patients and providers in order to prevent the acquisition and save the lives of people with this deadly yet treatable disease.

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CHAPTER 5: CONCLUSION

Cryptococcal meningitis (CM) is an infection of the brain caused by a fungus[1] and is responsible for 181,000 worldwide deaths per year.[2] Despite the widespread availability of antiretroviral therapy (ART), this opportunistic infection (OI) is still occurring. In 2016, treatment guidelines were updated for screening, testing, and treating CM in HIV-infected persons in Uganda.[3] An assessment of these guidelines found that the standard care for this disease was not implemented as a result of the lack of diagnostics, medications, and laboratory monitoring supplies at Lira Regional Referral Hospital (LRRH) in Lira, Uganda. In 2017, a CM Diagnosis and Treatment Program (CM-DTP) began in response to these findings to provide supplemental diagnostics, medications, laboratory tests, and supplemental staff for CM treatment and care.

After two years of program implementation, this dissertation evaluated whether the CM-DTP improved CM diagnosis and mortality outcomes when compared to a historical cohort of patients diagnosed with CM two years before program initiation. Overall improvements in CM treatment and care were also assessed. There was limited data regarding the experiences patients, family members, and providers encountered with CM treatment and care. Their experiences, perspectives, and recommendations are vital for the improvement of CM care and in order to reduce morbidity and mortality outcomes. To understand their perspectives, surveys and interviews with patients, family members, and healthcare providers were conducted to identify barriers and facilitators regarding CM treatment and care. The interviews were also used as a feedback tool to provide novel information on ways to improve CM care and the overall CM-DTP.

Impacts of the CM-DTP on Diagnosis, Treatment and CM Care

The results of the CM-DTP evaluation found increased CM diagnosis, decreased mortality trends, increased number of LPs performed, decreased use of overall antibiotics, and increased treatment with combination Amphotericin B (Ampho B) and fluconazole compared with the historical cohort. Some comparisons and analyses were not able to be performed on cofactors related to mortality because of the small sample sizes in the positive, confirmed CM groups (cohort 1: n=46 and cohort 2: n= 99). In addition, the analyses on mortality in cohort 2 found that some of the variables (e.g. hospitalized days, confusion, and GCS) were confounders on the independent variables of the LPs performed and antibiotics prescribed. These variables were controlled through logistic regression analyses. Comparisons of the positive and presumed CM group were more similar in size between cohorts 1 and 2 (n=127 vs. n=146), and mortality was significantly decreased between these cohorts (51.97% vs. 39.04%). Although many of our comparisons between cohorts among the positive CM group were not significantly different, improvements in mortality and diagnosis were evident based on observed trends between the two cohorts. The CM-DTP is still ongoing, and we recommend a re-evaluation when a larger sample is obtained in cohort 2. The new evaluation would increase our understanding of which factors of CM care were associated with mortality and what components of the program were most instrumental in improving CM outcomes at LRRH and in rural Uganda generally.

Barriers to CM Care Among Patients, Family Members, and Providers

We found several barriers to care that patients, family members, and providers faced when seeking or providing CM care. Key barriers were identified as a) lack of CM education, b) lack of knowledge or understating of CM, c) delays related to diagnosis and treatment and d) pre-existing mental health conditions.

Lack of Education and Knowledge

A key barrier was related to the lack of education and knowledge about CM for participants. Providers were candid about their lack of education and knowledge of CM. Many reported (80%) that they did not have any formal education on CM outside of their professional school setting. They also reported their lack of experience and knowledge, which decreased their ability to recognize or test for CM. Those who had the least amount of experience and knowledge were nurses who worked primarily in the health center III facilities.

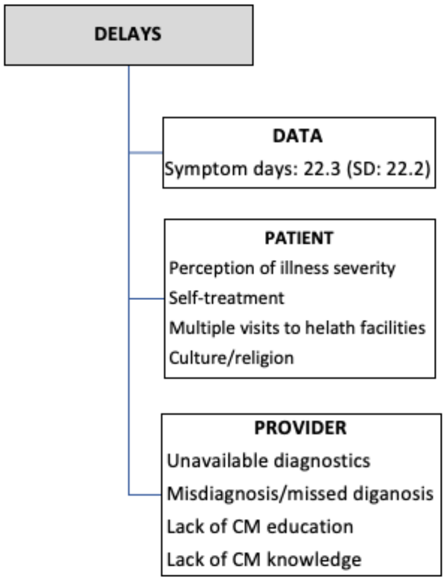
All patients and family members who participated in the study requested more education on CM, as most had not heard of this disease until their diagnosis. They shared that they did not know or understand the basics facts about CM– aside from their own personal learning with the disease. We found that a lack of patient education or understanding can contribute to false perceptions of illness severity and increase their risk for CM if they don't take their ART regularly. Additionally, the belief that providers know about CM and are educating patients about this disease brought greater clarity that this is not happening based on participant reports.

Delays to CM Diagnosis and Treatment

Another key barrier to care was the delay of presentation to care and the multiple visits to lower-level health centers before being diagnosed or treated for CM. Patients and family members reported the practice of self-treatment when symptoms first presented which supports their perception of decreased illness severity. Analysis from the CM-DTP found presentation delays to LRRH as patients had symptoms for over two weeks before coming to LRRH for CM diagnosis. Patient surveys identified a similar length of symptoms days before they sought evaluation at a health facility.

Many patients (95%) sought healthcare at lower-level health facilities several times before finally being diagnosed with CM and admitted to LRRH for treatment. This information supports that patients are seeking care at their local health facilities; however, it raises new issues of potential misdiagnosis or missed diagnosis by healthcare providers among patients who are seen multiple times before their CM diagnosis. Providers admitted that their lack of experience and knowledge about CM can lead to a missed diagnosis and reported how the lack of diagnostic tests limited their ability to make an accurate diagnosis of CM. Additionally, participants revealed that seeking care through alternative cultural treatments through witchdoctors and prayers also contributed to delays in CM diagnosis and treatment. The information provided by all participants gave greater clarity on how delays can occur. There is not a single cause for delays; rather, it is multifactorial, which includes issues surrounding patient and provider education and knowledge, cultural beliefs, and available supplies and diagnostics (Figure 5.1).

Figure 5.1. Factors for CM Delays



Mental Health Conditions

Another major barrier was the depression or anxiety patients experienced due to stigma related to their HIV status. Many patients experienced stigma, feeling shame and fear about their HIV diagnosis, inhibiting them from going to the ART clinic to pick up their ARVs. This barrier created by the stigma was associated with their HIV diagnosis which led to immunosuppression and increased risk for opportunistic infections like CM. There are currently no mental health screening requirements at LRRH or the clinical sites where this study was conducted. In Uganda, services for mental healthcare are limited due to a lack of providers, funding, and resources.

Facilitators of CM Care Among Patients, Family Members, and Providers

Participants also identified that key facilitators of CM care were available diagnostics and treatments, and support patients received from family, friends, and healthcare professions. Providers relayed that available diagnostics at their health facility would facilitate their ability to make timely and accurate diagnoses of CM. Having a diagnosis would also provide more certainty of what the next step in care should be, whether that includes treatment with antifungals or referral to a higher level of care.

Patient Support From Family, Friends, and Healthcare Providers

Participants acknowledged that having encouragement and support from the people around them were facilitators to continue to seek healthcare and to maintain their health. Having this support from friends, family members, and healthcare providers also instilled hope and a purpose for life.

Recommendations

The recommendations based on the dissertation results are to provide mental health screening at HIV clinic appointments to assess and address mental health issues which may include referrals to counseling or psychiatry or medications for mood disorders. Additionally, providing crucial diagnostic tests to the lower-level health facilities; where most of the patients are seeking their initial healthcare visit should be available. Diagnostic and treatments should also be available at the higher-level health centers and hospitals to treat all patients and not reserve appropriate care for only those who can afford treatment. Also, further investigation regarding the improvements in antibiotic stewardship and the associated financial benefits can be conducted through an economic evaluation. The analysis can provide evidence of cost-savings, which can help justify this program to become a part of the standard protocol for the facility, leading to the sustainability of the CM-DTP. Lastly, all participants should have education about CM, HIV misconceptions, and general awareness about CM. Developing an education curriculum and an awareness program on CM for patients, providers, and community members can bridge this knowledge gap and help improve timely recognition, diagnosis, and treatment for CM with the ultimate goal of saving lives. A comprehensive list of recommendations can be found in Appendix G.

Limitations

Collecting secondary data through patient hospital charts has inherent limitations to the quality and quantity of data collected, which was evidenced by missing data in patient charts. Documentation in the charts showed written orders for certain tests and treatments. Many charts, however, provided no evidence that tests were done or treatments given. Therefore, we cannot determine whether combination Ampho B and fluconazole were administered as a result of poor documentation, specifically in cohort 1. Additionally, morbidity outcomes were unable to be compared between cohorts, as morbidity data for cohort 1 was not available. Financial status also could have been a confounder for those in cohort 1, as patients were given appropriate treatments only if they were able to afford them. In cohort 2, all participants were given appropriate treatment, regardless of their financial ability.

For the mixed-methods analyses, recall bias may have been present because those who were treated for CM over two years ago may not have been able to recall details, such as dates and treatment, compared to participants who were seen within the past few months. For example, it was reported that the average symptoms days before seeing a health provider was 163 days for patients who died; however, data from the CM-DTP analysis (Chapter 2) reported that patients had an average of 19.2 symptom days. This discrepancy of symptom days between these two studies could suggest recall bias on the part of the family members reporting this information. Interviewer bias may have been present as well; those who were interviewed later in the study were asked more closed-ended questions based on common responses interviewers were hearing from previous study participants. A more comprehensive list of limitations can be found in Chapters 2, 3, and 4 of this dissertation.

Implications for Future Research

The findings from this dissertation identified gaps in overall CM care and other topics associated with CM. There are potential opportunities for follow-up interventions or studies to gain further understanding and improve CM care. Three key research areas emerged from this dissertation, including a) development of a CM education curriculum and awareness program for patients, providers, and community members, b) mental health screening and treatment for patients with HIV, and c) exploring the meningitis burden, cause, and outcomes in rural Uganda.

CM Education

This study obtained novel information, shared by participants regarding their experience with CM. Our understanding of the barriers and facilitators of CM care increased through the information from the surveys and interviews. A key finding was the lack of knowledge and education on the basics of CM, including its diagnosis and care, among both patients and providers. As such, the next phase of the CM-DTP should facilitate efforts to understand how to standardize CM education for providers and patients, including the topics which should be included (CM cause, prevention, diagnosis, treatments, treatment duration, symptoms, and long-term effects), what platform(s) should be used to disseminate this education, and the best ways to raise awareness about this disease in the general public. Education topics and implementation strategies need to be presented to the local health centers, the referral hospitals, and the Ministry of Health to develop clear and consistent information for all patients, providers, and community members.

Mental Health Screening

Stigma remains an evident barrier for ART, leading to issues of non-adherence. The ramifications of non-adherence to ART manifest in the development of opportunistic infections (OIs) among people living with HIV. Patients revealed that the effects of shame and fear caused by stigma led to mental health conditions such as depression and anxiety. Little research has been conducted on mental health issues within people diagnosed with CM or HIV in rural areas. Mental illnesses are still misunderstood in Uganda, yet it is impossible to ignore the mental, emotional, and psychological toll of being diagnosed with HIV/AIDS given the cultural stigma associated with this disease and that many of the patients are survivors of the decades-long civil war in this area of Uganda. Having mental health screenings for all new and existing patients living with HIV at ART clinics could identify underlying mental illnesses that could be treated with counseling or early medication therapy. Early detection and treatment could improve ART adherence and decrease the burden of CM and other OIs. A comprehensive list of recommendations from this dissertation can be found in Appendix G.

Meningitis Burden in Rural Uganda

The compilation of data from chart reviews revealed the burden of CM, as well as other potential forms of meningitis. Over one million people worldwide are infected with meningitis per year.[4] Our sample included 281 potential cases of CM; however, this number may not be accurate, since identifying non-fungal causes of meningitis is difficult because of the lack of diagnostic tests available. Currently, only gram stains for cerebral spinal fluid (CSF) are available in this area of Uganda, and this test cannot differentiate bacterial or viral species. Further research on meningitis causes can identify which types are most prevalent to inform interventions to implement. This level of specificity is required to prevent and accurately treat these causes and for mortality and morbidity outcomes to improve.

Implications for Nursing Practice

In Uganda, nurses make up the majority of the healthcare workforce[5] and are most commonly posted at lower-level health centers[6] as the primary care provider to diagnose and treat patients. Our study showed that patients went to these lower-level health facilities (HC II and III) as their first point of care for their early CM symptoms. It was also at these facilities where delays for diagnosis and treatment occurred. This study discovered that among the providers who refer patients to LRRH, all the nurses and the majority (80%) of other MOs and COs last had CM education during their initial training, which for some was decades ago. Additionally, nurses reported that of the various illnesses they see in patients, they had the least confidence in diagnosing and treating patients with CM.

These findings support the pressing need for CM education for health workers at the lower health facilities and the nurses who oversee those clinics. They are the first point of care for most CM patients. As such, they must know the clinical signs for CM to suspect this disease and initiate testing for timely diagnosis and treatment when it is easier to treat this disease. Providing education for nurses and other healthcare workers will give them the knowledge and confidence they need to a) diagnose and manage CM care or b) refer the patient to a higher level of care more quickly to preserve life and decrease morbidity outcomes. Nurses serve as both the backbone and the frontline of healthcare services delivery in Uganda. Because of this, improving their education and knowledge in CM is imperative to reduce mortality and morbidity outcomes.

Future Research and Training

Upon the completion of this dissertation, I will be returning to Uganda (post-COVID) as a Fulbright and Robert Wood Johnson Future of Nursing Fellow to continue the CM-DTP and expand the scope of research to all meningitis causes. I will be involved in a secondary data extraction investigating all-cause meningitis to assess the prevalence and etiologies of meningitis at LRRH using a rapid point-of-care diagnostic test and evaluate mortality outcomes. I will also be conducting an economic evaluation of the CM-DTP in conjunction with the all meningitis study. I hope to strengthen my proficiency as a global health researcher over the next two years before obtaining an assistant nursing professor position at a research university.

Conclusion

Important and novel information regarding CM care and treatment at LRRH was identified. The results suggested that the CM-DTP improved overall care related to diagnosis and treatment and showed a decreasing trend in mortality within the two years it has been implemented. The surveys and interviews conducted with patients, family members, and healthcare providers elucidated the perceived barriers and facilitators for CM care from their perspectives. The interviews also clarified some of the potential issues surrounding delays to care, which were formerly posited as patients delaying their care by not seeking treatment. However, this study proved that delays were multifactorial and that lack of CM education for both patients and providers was a primary factor in delayed care. These findings could not have been obtained through quantitative methods alone; the incorporation of qualitative methods brought clarity, context, and a richer understanding of the effectiveness of CM-DTP and the barriers and gaps that exist in CM care. The findings from this study can be used to provide future directions for research, improvements in nursing practice, and guide future interventions for education, diagnosis, and treatments for CM in order to save lives and restore patients' hope for life.

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APPENDIX A: Patient Survey

PATIENT	**SURVEY QUESTIONS**	
1.	What is your age?	**_______ Years**
2.	What is your gender?	**Male Female**
3.	What is your marital status?	**A) Married, living with partner** **B) Single, never married** **C) Separated** **D) Divorced** **E) Widowed**
4.	Where did you reside when you were treated for CM?	
5.	How long had you lived there?	
6.	What is the highest level of school you attended and completed (primary, secondary, higher)?	
7.	What is your employment status?	**A) Full time (40+ hours /week)** **B) Part time (<40 hours /week)** **C) Stay at home mom/dad** **D)Unemployed**
8.	What is your occupation?	
9.	What is your yearly income?	**__________________ Shillings**
10.	What referral hospital do you normally go to?	
11.	When were you at LRRH for CM treatment?	
12.		**CIRCLE THE BEST ANSWER**
13.	Before your diagnosis had you ever heard of Cryptococcal Meningitis?	**Yes No**
14.	Can you get CM again if you already had it?	**Yes No**
15.	What is CM caused by?	**A) Bacteria** **B) Virus** **C) Fungus** **D) Tuberculosis**
16.	What are some complications of CM?	**A) Vision Loss** **B) Hearing Loss** **C) Death** **D) All of the Above**
17.	If a member of your family got infected with HIV, would you want it to remain a secret or not?	**Yes No** **Don't know**
18.	If a member of your family became sick with HIV, would you be willing to care for her or him in your own household?	**Yes No** **Don't know**

19.	In your opinion, if a female teacher has HIV but is not sick, should she be allowed to continue teaching in the school?	**Yes** **No** **Don't know**
20.	Would you buy fresh vegetables from a shopkeeper or vendor if you knew that this person had HIV?	**Yes** **No** **Don't know**
21.	Do you think children living with HIV should be allowed to attend school with children who do not have HIV?	**Yes** **No** **Don't know**
22.	Do you think people hesitate to take an HIV test because they are afraid of how other people will react if the test result is positive for HIV?	**Yes** **No** **Don't know**
23.	Do people living with HIV, or thought to be living with HIV, lose the respect of other people?	**Yes** **No** **Don't know**
24.	Do people talk badly about people living with HIV, or who are thought to be living with HIV?	**Yes** **No** **Don't know**
25.	Do you fear that you could get HIV if you come into contact with the saliva of a person living with HIV?	**Yes** **No** **Don't know**
26.	Do you agree or disagree with the following statement: I would be ashamed if someone in my family had HIV.	**Agree** **Disagree**
27.		**SHORT ANSWER**
28.	What treatments did you use for the symptoms you had before coming to LRRH?	
29.	What symptoms did you experience which made you seek care at the clinic?	
30.	How long did you wait before you sought treatment for your symptoms?	
31.	After your symptoms appeared, if you saw a health care worker what did they diagnose you with?	
32.	What treatment did you get?	
33.	How many times did you see a healthcare provider or alternative therapist before you were seen at LRRH?	
34.	What did you like best about your experience with CM care at LRRH?	

35.	What did you like least about your experience with CM care at LRRH?	
36.	When were you diagnosed with ART?	
37.	Have you ever been on ART?	
38.	If yes, when were you started on ART?	
39.	Did you ever stop ART?	
40.	If yes, why did you stop?	
41.	When did you stop ART?	
42.	Did you ever restart ART?	
43.	If yes, when did you restart?	
44.	Are you currently on ART?	
45.	What ART clinic do you normally go to?	

APPENDIX B: Family Member Survey

FAMILY MEMBER	**SURVEY QUESTIONS**	
1.	What was your family member's age?	**______ Years**
2.	What was their gender?	**Male Female**
3.	What was their marital status?	**A) Married, living with partner** **B) Single, never married** **C) Separated** **D) Divorced** **E) Widowed**
4.	Where did they reside when they came to LRRH?	
5.	How long did they live there?	
6.	What was the highest level of school they attended and completed (primary, secondary, higher)?	
7.	What was their employment status?	**A) Full time (40+ hours /week)** **B) Part time (<40 hours /week)** **C) Stay at home mom/dad** **D)Unemployed**
8.	What was their occupation?	
9.	What was their yearly income?	**__________________ Shillings**
10.	What referral hospital did they normally go to?	
11.	When were they at LRRH for CM treatment?	
	FAMILY MEMBER KNOWLEDGE AND STIGMA	**CIRCLE THE BEST ANSWER**
12.	Before their diagnosis had you ever heard of Cryptococcal Meningitis?	**Yes No**
13.	Can you get CM again if you already had it?	**Yes No**
14.	What is CM caused by?	**A) Bacteria** **B) Virus** **C) Fungus** **D) Tuberculosis**
15.	What are some complications of CM?	**A) Vision Loss** **B) Hearing Loss** **C) Death** **D) All of the Above**
16.	If a member of your family got infected with HIV, would you want it to remain a secret or not?	**Yes No** **Don't know**

17.	If a member of your family became sick with HIV, would you be willing to care for her or him in your own household?	**Yes No** **Don't know**
18.	In your opinion, if a female teacher has HIV but is not sick, should she be allowed to continue teaching in the school?	**Yes No** **Don't know**
19.	Would you buy fresh vegetables from a shopkeeper or vendor if you knew that this person had HIV?	**Yes No** **Don't know**
20.	Do you think children living with HIV should be allowed to attend school with children who do not have HIV?	**Yes No** **Don't know**
21.	Do you think people hesitate to take an HIV test because they are afraid of how other people will react if the test result is positive for HIV?	**Yes No** **Don't know**
22.	Do people living with HIV, or thought to be living with HIV, lose the respect of other people?	**Yes No** **Don't know**
23.	Do people talk badly about people living with HIV, or who are thought to be living with HIV?	**Yes No** **Don't know**
24.	Do you fear that you could get HIV if you come into contact with the saliva of a person living with HIV?	**Yes No** **Don't know**
25.	Do you agree or disagree with the following statement: I would be ashamed if someone in my family had HIV.	**Agree** **Disagree**
		SHORT ANSWER
26.	What treatments did they use for the symptoms they had before coming to LRRH?	
27.	What symptoms did they experience which made them seek care at the clinic/hospital?	
28.	How long did they wait before they sought treatment for their symptoms?	
29.	After their symptoms appeared, if they saw a health care worker what did they diagnose them with?	
30.	What treatment did they get?	
31.	How many times did they see a healthcare provider or alternative therapist before they were seen at LRRH?	

32.	What did you like best about their experience with CM care at LRRH?	
33.	What did you like least about their experience with CM care at LRRH?	
34.	When were they diagnosed with ART?	
35.	Were they ever on ART?	
36.	If yes, when were they started on ART?	
37.	Did they ever stop ART?	
38.	If yes, why did they stop?	
39.	When did they stop ART?	
40.	Did they ever restart ART?	
41.	If yes, when did they restart?	
42.	Were they on ART when they died?	
43.	What ART clinic do they normally go to?	

APPENDIX C: Provider Survey

PROVIDER	**SURVEY QUESTIONS**	
1.	What is your age?	**______ Years**
2.	What is your gender?	**Male Female**
3.	What is your marital status?	**A) Married, living with partner** **B) Single, never married** **C) Separated** **D) Divorced** **E) Widowed**
4.	Where do you currently reside?	
5.	How long have you lived there?	
6.	What is the highest level of school you attended and completed (primary, secondary, higher)?	
7.	What is your employment status?	**A) Full time (40+ hours /week)** **B) Part time (<40 hours /week)** **C) Stay at home mom/dad** **D) Unemployed**
8.	What is your occupation?	
9.	How long have you worked at this facility?	**_________________ Shillings**
10.	What is your estimated yearly income?	
		CIRCLE THE BEST ANSWER
11.	What is Cryptococcal meningitis caused by?	**A) *Bacteria*** **B) *Virus*** **C) *Fungus*** **D) None of the above**
12.	How is CM contracted?	**A) *Contact*** **B) Sexual *contact*** **C) *Airborne*** **D) *Blood***
13.	Who is most susceptible to CM	**A) Men** **B) Immunocompromised** **C) Children** **D) Any person**

14.	How long is maintenance therapy given to prevent relapse of CM?	**A) One month** **B) One year** **C) 6 months** **D) CD4 ≥ 200**
15.	What is the best way to diagnose CM?	**A) Culture** **B) India Ink** **C) Lateral flow assay *(LFA*)** **D) I don't know**
16.	How available is amphotericin B in your area?	**A) Not available** **B) Sometime available** **C) Always available**
17.	If a member of your family got infected with the AIDS virus, would you want it to remain a secret or not?	**Yes No** **Don't know**
18.	If a member of your family became sick with the virus that causes AIDS, would you be willing to care for her or him in your own household?	**Yes No** **Don't know**
19.	In your opinion, if a female teacher has the HIV but is not sick, should she be allowed to continue teaching in the school?	**Yes No** **Don't know**
20.	Would you buy fresh vegetables from a shopkeeper or vendor if you knew that this person had the HIV?	**Yes No** **Don't know**
21.	Do you think children living with HIV should be allowed to attend school with children who <u>do not</u> have HIV?	**Yes No** **Don't know**
22.	Do you think people hesitate to take an HIV test because they are afraid of how other people will react if the test result is positive for HIV?	**Yes No** **Don't know**
23.	Do people living with HIV, or thought to be living with HIV, lose the respect of other people?	**Yes No** **Don't know**
24.	Do people talk badly about people living with HIV, or who are thought to be living with HIV?	**Yes No** **Don't know**
25.	Do you fear that you could get HIV if you come into contact with the saliva of a person living with HIV?	**Yes No** **Don't know**

26.	Do you agree or disagree with the following statement: I would be ashamed if someone in my family had HIV.	**Agree** **Disagree**
27.	If a member of your family got infected with the AIDS virus, would you want it to remain a secret or not?	**Yes No** **Don't know**
28.	Do you screen for cryptococcal disease in your facility?	**Yes No**
		SHORT ANSWER
29.	At what CD4 should you screen for CM?	
30.	Name the 5 most common symptoms of CM?	
31.	Who do you screen?	
32.	What treatment do you give most often for CM?	
33.	What do you need to diagnose CM more accurately?	
34.	What symptoms does a patient need for you to think it might be CM?	
35.	How often do you educate your patients about their diagnosis or condition?	
36.	What prevents you from providing education to your patients?	

APPENDIX D: Patient Semi-Structured Interview Questions

PATIENT	INTERVIEW QUESTIONS
1.	What happened to you for you to seek treatment at LRRH?
2.	Did you seek treatment on your own? If no, why not?
3.	Did anyone encourage you to seek treatment? Whom and when?
4.	How did they encourage you?
5.	How has HIV stigma affected your ability to go to the clinic and take your meds?
6.	What are the pluses of going to the clinic?
7.	What are the minuses of going to the clinic?
8.	Who goes to the clinic with you?
9.	What made it difficult to seek treatment?
10.	What are you doing now to prevent CM from coming back again?
11.	How often do you take your CM medication?
12.	How important is it for you take your ART and fluconazole daily?
13.	Now that you know about CM and experienced it, what would you do differently to try to prevent it?
14.	Can you tell me when you were first diagnosed with HIV?
15.	Can you tell me about how you were first diagnosed with HIV?
	ONLY ASK QUESTIONS 16-23 IF STARTED ON HIV MEDS
16.	When were you started on HIV treatment?
17.	How often did you take your HIV medication?
18.	Do you believe your HIV medication can improve your health?
19.	What makes it easier to take your HIV medications?
20.	What makes it hard to take your HIV medications?
21.	What makes it easier to get your HIV medications
22.	What makes it hard to get your HIV medications?
23.	How often do you take your HIV medication?
24.	How was your experience with CM care at LRRH?
25.	What did you learn about CM now that you've experienced it?
26.	What would have made your experience better during your hospitalization?
27.	Is there any other feedback you want to give or questions you have?

APPENDIX E: Family Member Semi-Structured Interview Questions

FAMILY MEMBER	INTERVIEW QUESTIONS
1.	What happened to your family member for them to seek treatment at LRRH?
2.	Did they seek treatment on their own? If no, why not?
3.	Did anyone encourage them to seek treatment? Whom and when?
4.	How were they encouraged?
5.	How did HIV stigma affect their ability to go to the clinic and take their meds?
6.	Who went to the clinic with them?
7.	What made it difficult to seek treatment?
8.	How often did they take their CM medication?
9.	How important was it for them take to take their ART and fluconazole daily?
10.	Can you tell me when they were first diagnosed with HIV?
11.	Can you tell me about how they were first diagnosed with HIV?
	ONLY ASK QUESTIONS 15-22 IF STARTED ON HIV MEDS
12.	When were they started on HIV treatment?
13.	How often did they take their HIV medication?
14.	Did they believe their HIV medication could improve their health?
15.	What made it easier to take their HIV medications?
16.	What made it hard to take their HIV medications?
17.	What made it easier to get their HIV medications
18.	What made it hard to get their HIV medications?
19.	How often do they take their HIV medication?
20.	How was your experience with CM care?
21.	What did you learn about CM now that you've experienced it with your family member?
22.	What would have made their experience better during their hospitalization?
23.	Is there any other feedback you want to give or questions you have?

APPENDIX F: Provider Semi-Structured Interview Questions

PROVIDER	INTERVIEW QUESTIONS
1.	What disease or illnesses do you feel you need more information on?
2.	How important is it for you to know about CM?
3.	How confident are you to be able to accurately diagnose CM?
2.	What makes it easy to diagnose CM
3.	What makes it difficult to diagnose CM
4.	What prevents you from diagnosing patients for CM?
5.	How do you get access to the items you need to diagnose or treat your patients for CM?
6.	What are other ways you can get the supplies you need for diagnosis and treatment for CM patients?
7.	What is the importance to diagnose a patient correctly with CM?
8.	What does a patient need to look like before you refer them to LRRH?
9.	What type of patient gets CM?
10.	What prevents you from treating patients with CM or cryptococcal disease?
11.	Please describe your CM training to me.
12.	How often do you review the guidelines for CM screening and treatment?
13.	What should patients know to help improve outcomes of CM?
14.	What should providers know to help improve outcomes of CM?
15.	What should CM patients do to improve their morbidity and mortality outcomes?
16.	How can providers improve CM morbidity and morbidity?
17.	Whose responsibility is it to educate patients?
18.	How important is it for you to provide education to your patients?
19.	What recommendations do you have to make CM education easier for providers?
20.	What recommendations do you have to decrease barriers to CM diagnosis and treatment for yourself and patients?
21.	Is there any other feedback you want to give or questions you have?

APPENDIX G: Key Recommendations of the Mixed Methods CM-DTP Evaluation