CRYPTOSPORIDIOSIS AMONG HIV PATIENTS PRESENTING WITH DIARRHOEA BETWEEN SEPTEMBER TO DECEMBER, 2012 IN SPECIALIST HOSPITAL SOKOTO, NIGERIA.

BY

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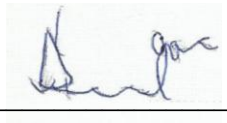
FEBRUARY, 2014

DECLARATION

I hereby declare that the reported in this thesis was carried out by me under the supervision of Dr. Sani Mohammed Shehu and Dr. Saad Aliyu Ahmed of Department of Pathology, Faculty of Medicine, Ahmadu Bello University, Zaria.

No part of this work has been presented in any previous application for higher degree.

The works of other investigators are referred to and acknowledged accordingly.



ABUBAKAR ALIYU DANMAFARA

CERTIFICATION

This thesis entitled "**CRYPTOSPORIDIOSIS AMONG HIV PATIENTS PRESENTING WITH DIARRHOEA IN SPECIALIST HOSPITAL SOKOTO, NIGERIA"** by ABUBAKAR Aliyu Danmafara meets the regulations governing the award of the degree of Master in Public Health of Ahmadu Bello University, Sokoto, and is approved for its contribution to knowledge and literary presentation..

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DEDICATION

This work is dedicated to my parents for their contribution to my academic and professional carrier, and to my wife and children for their patience and understanding.

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As the saying goes “Whatever has a beginning must surely have an end”. And all things are possible only by the will of God Almighty”. Today just like the blink of an eye, God has made me witness the completion of my study by His Grace. All Glory and thanks are due to Him and Him alone through his infinite mercies He granted me the health, strength and wisdom to complete this work surely, none is worthy of worship but God.

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Acronyms and Abbreviations

ABC	Abacavir
AFB	Acid-fast bacilli
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase (a liver function test)
ARV	Antiretroviral (drugs)
ART	Antiretroviral Therapy
AZT	azidothymidine—chemical name for the generic zidovudine (Also called ZDN)
BCG	Bacille Calmette-Guerin
CDC	Centre for Disease Control
CIDA	Canadian International Development Agency
CD4	Count of the lymphocytes with a CD4 surface marker per cubic millimetre of blood (mm^3)
CHEW	Community Health Extention Worker
D4T	stavudine
DDI	didanosine
DOT	Directly Observed Treatment
DOTS	Directly Observed Treatment(short course)
EFV	efavirenz
FDC	Fixed drug combination
H	Isoniazid (INH)

HCT	HIV Testing and Counselling
HIV	Human Immunodeficiency Virus
IDV/r	Idinavir/retonavir
IHVN	Institute of Human Virology of Nigeria
IMAI	Integrated Management of Adolescent and Adult Illness
IMCI	Integrated Management of Childhood Illness
INH	Isoniazid
LPV/r	Lopinavir/retonavir
MDR	Multiple drug resistant (TB)
NFV	nelfinavir
NVP	Nevirapine
OI	Opportunistic Infection
PMTCT	Prevention of Mother to Child Transmission (of HIV)
PEP	Post-Exposure Prophylaxis
Rx	Treatment
TB	Tuberculosis
TDB	tenofovir
TLC	Total Lymphocyte Count
XDR	Extensive drug resi

Summary

Diarrhoea remains one of the most important health problems globally and a leading cause of morbidity and mortality among immuno compromised individuals. It accounts for over 50 million deaths (in all ages) world-wide and it ranks 3rd among diseases responsible for human mortality globally[1.]

This study was carried out to determine the prevalence of *Cryptosporidium parvum* infection among HIV patients visiting the Specialist Hospital Sokoto (SHS), Nigeria. A total of 150 stool samples were examined for oocysts of *C. parvum* using the Stool concentration technique and modified Zeil-Neilson staining technique. 85 females and 65 males were tested.

The overall parasite prevalence of Human intestinal parasites encountered in the study was 22.7% (34/150) with *Cryptosporidium parvum* 4.0%, being the highest compared to other parasites. The age group distribution of Cryptosporidium prevalence among HIV infected patients who had diarrhoea was 4.0%. With the highest prevalence among patients aged 46-55years when compared to 0.0 % prevalence recorded in those aged 6 -15, 16 – 25 and 56 -60. Crypto was commoner among female patients (2.6) when compared to the male (1.4) prevalence. There is no significant statistical difference between the two groups at 95 % Confidence. Limit. The observed monthly prevalence of Crypto among the vulnerable group was observed to be high in the month of November. There is significant statistical difference between all the four at 95% confidence limit. On the other hand, the prevalence of Crypto among different drugs regiment (combination) was found to be higher among Regimen 1A. The observed prevalence among CD4 groups showed higher prevalence 2.7 % among HIV patients with diarrhoea whose CD4 were

below 350 who at the same time formed majority of the patients tested (139 patients) compare to the least prevalence 1.3 % recorded among patients with CD4 greater than 350. There is observed significant statistical difference between the two categories. 4.0 % of crypto encountered among HIV patients with diarrhea and blood only, OR 1.03, 95% CI 0.20 85.27, P - value 0.7 when compared to 0.0 % Crypto prevalence recorded among diarrhea with blood and mucus and diarrhea with mucus only.

From the result of this study, Crypto was therefore found to be associated with HIV diarrhoea particularly in the advanced stage of the infection as *Cryptosporidium* Oocysts have been demonstrated in faeces of HIV infected patients attending Specialist Hospital. It accounts for 4.0% of diarrhoeal cases among this group. This study provides baseline data on the prevalence of Cryptosporidiosis among HIV infected patients presenting with diarrhea and the relationship between CD4 and ART regimen. It is therefore recommended that information and findings obtained from this study be considered in planning interventions aimed at managing diarrhoea diseases among HIV and other immuno-suppressed patients.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background Information

Diarrhoea remains one of the most important health problems globally and a leading cause of morbidity and mortality among immuno compromised individuals. It accounts for over 50 million deaths (in all ages) world-wide and it ranks 3rd among diseases responsible for human mortality globally. Diarrhoea or looseness of the bowels is increased frequency, fluidity or volume of bowel movements compared to usual. Most people have occasional attacks of acute diarrhoea, usually caused by contaminated food or water or excessive alcohol consumption. Such attacks normally clear up within a day or two, whether or not they are treated. Chronic diarrhoea, on the other hand, may be the result of a serious intestinal disorder or of more general disease. The commonest cause of acute diarrhoea is food poisoning; the organisms involved usually being *Staphylococcus, Clostridium, Salmonella, E. coli O157, Campylobacter, Cryptosporidium,* and *Norwalk virus*. A person may also acquire infective diarrhoea as a result of droplet infections from adenoviruses or echoviruses. [1, 2]

The involvement of protozoan agents in humans can be traced back to the 19th Century and this group constitutes the highest group of parasites known to be associated with diarrhoeal condition. Originally the coccidian parasites are known to be pathogenic mainly to some species among the lower animals, insects, birds, and human primates.[2] Traditionally dirrhoeal Protozoan agents are *Giardia lamblia, Entamoeba histolytica, Balantidium coli* and Coccidian agents like *Isospora belli, Cyclospora cayetenensis Microsporidia* and, *Cryptosporidium parvum*[3, 4, 5 ,6, 7, 8].

Chronic diarrhoea occurs in up to 70% of patients infected with HIV in Africa[9]. Cryptosporidiosis, also known as crypto[10,] is a parasitic disease caused by *Cryptosporidium,* a protozoan parasite in the phylum Apicomplexa. It affects the intestines of mammals. It is spread though the fecal-oral route, often through contaminated water[10]. The main symptom is self-limiting diarrhoea in people with intact immune systems. In immune compromised individuals, such as AIDS patients, the symptoms are particularly severe and often fatal. *Cryptosporidium* is the organism most commonly isolated in HIV positive presenting with diarrhoea. Treatment is symptomatic, with fluid rehydration, electrolyte correction and management of any pain. [10]

Despite not being identified until 1976, it is one of the most common waterborne diseases and is found worldwide. The parasite is transmitted by environmentally hardy microbial cysts (Oocysts) that, once ingested, exist in the small intestine and result in an infection of intestinal epithelial tissue. The incubation period is usually about one week, with clinical signs of profuse, offensive, watery diarrhoea, which may be accompanied by abdominal pain, vomiting and fever. [11], [12] *Cryptosporidium* is known to be common in food and water and are spread by ingestion of these organisms (and others), primarily contracted through drinking water, the prevention and control of this parasite has become a public health concern. Prevention methods include the installation of more advanced filtration systems, constant testing of water supply, and educating populations about the signs of the disease and ways to prevent it as Cryptosporidiosis difficult to treat.[13]

1.2 Statement of Problem

In 2004, cryptosporidiosis was added to the WHO's 'Neglected Diseases Initiative' which includes diseases that occur mainly in developing countries and are linked to poverty and lack of access to services. In the absence of a universal treatment program and with the lack of access to

care, cryptosporidiosis continues to be a major opportunistic infection and an important cause of morbidity and mortality in persons living with HIV/AIDS in developing countries[14]. Together with the lack of effective specific treatment for cryptosporidiosis in immuno compromised patients, this underscores the critical importance of continuing efforts to develop strategies to prevent and treat this disease in vulnerable populations particularly in Nigeria where Cryptosporidium was shown to be a significant agent of diarrhoea among immune competent patients in our hospitals[14], and [15], there are few studies that have been done on the significance of *Cryptosporidium* in HIV/AIDS related diarrhoea. Considering the alarming rate at which HIV is spreading among the populace, a nationwide conceited effort is required to establish its incidence. The disease initially thought to be self-limiting in immune competent patients now assumes a chronic course in malnourished and immune compromised patients[14].

It is in view of the above that the study sets to investigate the occurrence and impact of *Cryptosporidium* among HIV/AIDS patients accessing services at the HIV/AIDS Comprehensive Centre of the Specialist Hospital Sokoto.

1.3 Justification

Though this study was limited to People Living with HIV/AIDS accessing services at the Specialist Hospital Sokoto alone, data generated from this study when related to similar works across the country such as work carried out on Prevalence of Cryptosporidium infection among undernourished children in Jos, Central Nigeria[15] and Apparent rarity of cryptosporidiosis in Human Immunodeficiency Virus (HIV)-related diarrhoea in Enugu, South-Eastern Nigeria [16] , could give an overall incidence/impact of this parasite on these vulnerable group-HIV/AIDS

patients. It is believed that data from this study may provide adequate basis for evolving sustainable cost-effective control measures in our environment

1.4 Research Question.

The research questions for this study are;

1. Is cryptosporidiosis associated with diarrhoea among HIV patients presenting with diarrhoea visiting the Sokoto state specialist?
2. What is the relationship between stages of HIV infection, clients CD4 status, stool nature and cryptosporidiosis among HIV patients presenting with diarrhoea?

1.5 General and Specific Objectives

1.5.1 General Objectives

The main objective of the study is to determine the prevalence of *Cryptosporidium* amongst HIV/AIDS patients presenting with diarrhoea attending Specialist Hospital, Sokoto.

1.5.2 Specific Objectives

a. To determine the prevalence of cryptosporidiosis among HIV patients presenting with diarrhoea
b. To determine the prevalence of cryptosporidiosis among HIV patients presenting with diarrhoea in relation to patient's sex, age and other human intestinal parasites.
c. To determine the prevalence of cryptosporidiosis among TB/HIV Co infected patients presenting with diarrhoea.
d. To relate the prevalence of cryptosporidiosis among HIV patients with diarrhoea to their CD4 status, drug regimen and stool nature.

1.6 Hypothesis; Null Hypothesis;

Cryptosporidiosis is associated with diarrhoea among HIV patients visiting the comprehensive HIV services center in specialist hospital Sokoto

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Cryptosporidiosis

Cryptosporidium spp. are intestinal protozoan parasites of the phylum Apicomplexa, which cause diarrheal disease in humans worldwide.[1] In immunocompetent individuals, infection with this parasite may be asymptomatic or cause a self-limiting diarrheal illness. However, in immunocompromised patients such as those with HIV/AIDS *Cryptosporidium* spp. may cause severe, chronic and possibly fatal diarrhea and wasting. Although *Cryptosporidium* was discovered in 1907, it was not till 1976 that the first human cases of cryptosporidiosis were reported and not till the onset of the AIDS epidemic in the early 1980s that this parasite became widely recognized as a human pathogen. [2]

Indeed, cryptosporidiosis was one of the original AIDS-defining illnesses and as such was associated with an increased risk of death compared to other AIDS-defining illnesses. [3] The use of highly active antiretroviral therapy (HAART) in the past 2 decades has reduced the prevalence of this disease in AIDS patients in industrialized countries. However, the emergence of drug-resistant HIV variants and failure or discontinuation of HAART has been associated with re-emergence of *Cryptosporidium* spp. infection in this patients.[4]

Even patients with advanced AIDS who are on HAART have recently been reported to have *Cryptosporidium* spp. Infection[15]. Although antiretroviral treatment (ART) has recently become available in some developing countries it is not widely available or affordable in most areas where the burden of HIV/AIDS is the greatest. In the absence of ART, HIV-infected patients are

subject to a cumulative lifetime incidence of diarrhea estimated at up to 100% in developing countries[16] with chronic diarrhea affecting up to 76% of patients with AIDS. [8]

Gastrointestinal and hepatobiliary disorders are among the most frequent complaints in patients with HIV disease. Advances in antiretroviral therapy are changing the nature of HIV disease and affecting many of the gastrointestinal manifestations. Before combination antiretroviral therapy, the best estimates suggested that 50 to 93% of all patients with HIV disease had marked GI symptoms during the course of their illness. Recent clinical experience suggests that effective anti-HIV therapy and chemoprophylaxis for *Pneumocystis carinii* (PCP), *Mycobacterium avium* (MAC), and cytomegalovirus (CMV) may delay/prevent the occurrence of gastrointestinal opportunistic infections. Given fewer late-stage immune compromised patients, clinicians must recognize the shifts in the spectrum of pathogens, recognize the need to maintain good nutrition, and facilitate outpatient management directed at identifying treatable causes and ameliorating symptoms.[9]

In 2004, cryptosporidiosis was added to the WHO's 'Neglected Diseases Initiative' which includes diseases that occur mainly in developing countries and are linked to poverty and lack of access to services[1]. In the absence of a universal treatment program and with the lack of access to care, cryptosporidiosis continues to be a major opportunistic infection and an important cause of morbidity and mortality in persons living with HIV/AIDS in developing countries. Together with the lack of effective specific treatment for cryptosporidiosis in immuno compromised patients, this underscores the critical importance of continuing efforts to develop strategies to prevent and treat this disease in vulnerable populations. Here we review the current state of knowledge about cryptosporidiosis in patients with HIV/AIDS, with a focus on studies from developing countries.

In addition, since knowledge of protective immune responses is essential for developing immune-based interventions such as vaccines and immunotherapy, we review what is known about immune responses in cryptosporidiosis, focusing on recent studies[2].

Cryptosporidium, also known as crypto, is a parasitic disease caused by *Cryptosporidium,* a protozoan parasite in the phylum *Apicomplexa.* It affects the intestines of mammals and is typically an acute short-term infection. It is spread through the fecal-oral route, often through contaminated water[10]. The main symptom is self-limiting diarrhoea in people with intact immune systems. In immuno compromised individuals, such as AIDS patients, the symptoms are particularly severe and often fatal, *Cryptosporidium* is the organism most commonly isolated in HIV positive patients presenting with diarrhoea. Treatment is symptomatic, with fluid rehydration, electrolyte correction and management of any pain. Despite not being identified until 1976, it is one of the most common waterborne diseases and is found worldwide. The parasite is transmitted by environmentally hardy microbial cysts (Oocysts) that, once ingested, exist in the small intestine and result in an infection of intestinal epithelial tissue depending on stages of HIV infection which are;

2.1.1 Diarrhoea among HIV Positive persons

Gastrointestinal (GI) manifestations of HIV disease include diarrhea, dysphagia and odynophagia, nausea, vomiting, weight loss, abdominal pain, anorectal disease, jaundice and hepatomegaly, GI bleeding, interactions of HIV and hepatotropic viruses, and GI tumors (Kaposi's sarcoma and non-Hodgkin's lymphoma). The evaluation of specific gastrointestinal complaints must be based on an assessment of the degree of immune suppression. Progressive immune compromise is associated with increasing prevalence of GI symptoms and remains the common endpoint for most individuals infected with HIV.[10]

Diarrhea is the most common GI symptom in patients with HIV. In outpatient studies, the prevalence of diarrhea ranged from 0.9 to 14%. Prevalence was increased in homosexual men and individuals with lower CD4 cell counts. In hospitalized individuals with advanced HIV, 50% of all patients had diarrhea.[5] Furthermore, there is considerable geographic variation in the frequency of diarrhea and the spectrum of enteric pathogens.

Among the more difficult management issues in the HIV-infected patient is deciding how extensively to investigate GI symptoms. The clinician must always weigh the discomfort and invasiveness of a procedure against the severity of the patient's complaints and the likelihood of identifying a treatable condition. Thus, for example, patients who are incapacitated by abdominal pain or diarrhea should be evaluated more extensively with endoscopic or imaging studies than patients whose symptoms do not interfere with daily activities[10]

2.1.2 Evaluation of Diarrhoea

Before undertaking an extensive evaluation of diarrhea, clinicians should obtain a careful history to exclude medications, lactose or food/fatty food intolerance, inadvertent use of cathartics (e.g., megadoses of vitamin C, lactose-containing medications, sorbitol-containing foods), and symptoms suggestive of a systemic infection or neoplasm. Unfortunately, the clinical history alone is not likely to establish a specific diagnosis when due to infection. A careful history can aid in localizing the segment of luminal GI tract most severely involved. For example, symptoms of cramps, bloating, and nausea suggest gastric or small-bowel involvement, or both, raising the possibility of infection with *Cryptosporidium*, *Microsporidium*, *Isospora belli*, or *Giardia* organisms.[7],[11]

Hematochezia and tenesmus imply large-bowel inflammation resulting from CMV, *Shigella*, *Campylobacter*, or *Clostridium* infections. Tenesmus can occur as a result of herpes, *Shigella*, or *Campylobacter* infections. The character, frequency, color, and odor of the stool are relatively nonspecific in HIV-related GI syndromes and are therefore of little value in identifying specific infections. A history that includes multiple sexual contacts or receptive anal sex increases the possibility of sexually transmitted diarrheal pathogens. The physical examination also provides few diagnostic clues in the evaluation of HIV-related diarrhea. Lymphadenopathy, hepatosplenomegaly, and abdominal tenderness have little diagnostic value.[11]

The most important goal in evaluating diarrhea in patients with HIV disease is to identify treatable infections or neoplasms with the minimum work-up necessary. Once dietary causes and medications are excluded, the initial evaluation should include stool culture for enteric bacteria, a specimen for *Clostridium difficile* toxin (in the setting of antibiotic use), and at least three stool specimens for ova and parasite examination (including acid-fast bacilli and trichrome stain). The importance of obtaining multiple specimens was re-affirmed in a recent study of 30 patients with a confirmed diagnosis of cryptosporidiosis. Only 53% of individual stool samples were positive, whereas 22 of 30 patients had at least one positive of three or more stool specimens tested. [1]

If a diagnosis is not reached following careful stool analysis, sigmoidoscopy is appropriate to identify CMV infection. Biopsies should be obtained from abnormal regions or randomly from rectal mucosa if no abnormalities are apparent. Although colonoscopy has been advocated instead of sigmoidoscopy for diagnosis of isolated right colonic CMV this approach is not likely to be as cost-effective as reserving the colonoscopy for patients in whom sigmoidoscopy is non diagnostic. If sigmoidoscopic evaluation is negative, upper endoscopy or colonoscopy with

intubation and biopsy of the terminal ileum may occasionally uncover small-bowel infection by *Cryptosporidium*, *Microsporidium*, or *M. avium*. A small-bowel biopsy should be obtained in any HIV-infected patient undergoing upper endoscopy for evaluation of diarrhea; this method has largely supplanted small-bowel capsule biopsies. Duodenal fluid can also be aspirated during endoscopy and examined for protozoal infection or small-bowel overgrowth. Compared with endoscopic procedures, the diagnostic value of radiographic contrast studies in evaluating diarrhea is very low and therefore these studies are not indicated. [2]

2.2 Stages of HIV/ Opportunistic Infections

2.2.1 Primary HIV infection

This stage of infection lasts for a few weeks and is often accompanied by a short flu-like illness. In up to about 20% of people the HIV symptoms are serious enough to consult a doctor, but the diagnosis of HIV infection is frequently missed. During this stage there is a large amount of HIV in the peripheral blood and the immune system begins to respond to the virus by producing HIV antibodies and cytotoxic lymphocytes. This process is known as sero conversion. If an HIV antibody test is done before sero conversion is complete then it may not be positive[17].

2.2.2 Stage 2: Clinically asymptomatic stage

This stage lasts for an average of ten years and, as its name suggests, is free from major symptoms, although there may be swollen glands. The level of HIV in the peripheral blood drops to very low levels but people remain infectious and HIV antibodies are detectable in the blood, so antibody tests will show a positive result. Research has shown that HIV is not dormant during this stage, but is very active in the lymph nodes. A test is available to measure the small amount

of HIV that escapes the lymph nodes. This test which measures HIV RNA (HIV genetic material) is referred to as the viral load test, and it has an important role in the treatment of HIV infection[17].

2.2.3 Stage 3: Symptomatic HIV infection

Over time the immune system becomes severely damaged by HIV. This is thought to happen for three main reasons:

- The lymph nodes and tissues become damaged or 'burnt out' because of the years of activity;
- HIV mutates and becomes more pathogenic, in other words stronger and more varied, leading to more T helper cell destruction;
- The body fails to keep up with replacing the T helper cells that are lost.

Antiretroviral treatment is usually started once an individual's CD4 count (the number of T helper cells) drops to a low level, an indication that the immune system is deteriorating. Treatment can stop HIV from damaging the immune system; therefore, HIV-infected individuals on treatment usually remain clinically asymptomatic[18].

However, in HIV-infected individuals not receiving treatment or on treatment that is not working, the immune system fails and symptoms develop. Initially many of the symptoms are mild, but as the immune system deteriorates the symptoms worsen. Symptomatic HIV infection is mainly caused by the emergence of certain opportunistic infections that the immune system would normally prevent. This stage of HIV infection is often characterized by multi-system disease and infections can occur in almost all body systems.[18]

Treatment for the specific infection is often carried out, but the underlying cause is the action of HIV as it erodes the immune system. Unless HIV itself can be slowed down the symptoms of immune suppression will continue to worsen[19].

2.2.4 Stage 4: Progression from HIV to AIDS

As the immune system becomes more and more damaged the individual may develop increasingly severe opportunistic infections and cancers, leading eventually to an AIDS diagnosis. A clinical criteria is used by WHO to diagnose the progression to AIDS, this differs slightly between adults and children under five. In adults and children (aged 5 or over) the progression to AIDS is diagnosed when any condition listed in clinical stage 4 is diagnosed and/or the CD4 count is less than 200 cells/mm^3 or a CD4 percentage less than 15. In children younger than five, an AIDS diagnosis is based on having any stage 4 condition and/or a CD4 percentage less than 20 (children aged 12-35 months) and a CD4 percentage less than 25 (children less than 12 months). The criteria for diagnosing AIDS may differ depending on individual country guidelines[19].

In our bodies, we carry many germs – bacteria, protozoa, fungi, and viruses which when our immune system is working, it controls these germs but when the immune system is weakened by HIV disease, these germs can get out of control and cause health problems. Infections that take advantage of weakness in the immune defences are called "opportunistic". The phrase "opportunistic infection" is often shortened to "OI" [19]

People who aren't HIV-infected can develop OIs if their immune systems are damaged as HIV weakens the immune system so that opportunistic infections can develop. When some one is

HIV-infected and develop opportunistic infections, he might have AIDS [19]. WHO recommends HIV testing of TB patients and TB screening for all HIV-infected persons is therefore recommended [19]

2.3 HIV/AIDS Opportunistic Infections

In our bodies, we carry many germs – bacteria, protozoa, fungi, and viruses. When our immune system is working, it controls these germs. But when the immune system is weakened by HIV disease or by some medications, these germs can get out of control and cause health problems.

2.3.1 Classifications of opportunistic infections

In the early years of the AIDS epidemic, OIs caused a lot of sickness and deaths. Once people started taking strong antiretroviral therapy (ART), however, a lot fewer people got OIs. It's not clear how many people with HIV will get a specific OI. In women, health problems in the vaginal area may be early signs of HIV. These can include pelvic inflammatory disease and bacterial vaginosis, among others. The most common OIs are listed here, along with the disease they usually cause, and the CD4 cell count when the disease becomes active:

Cytomegalovirus (CMV) is a viral infection that causes eye disease that can lead to blindness.CD4 cell range: under 50.

1. Candidiasis (Thrush) is a fungal infection of the mouth, throat, or vagina. CD4 cell range: can occur even with fairly high CD4 cells. A person who has unsafe sex is at risk of several STIs and other than HIV, STIs are common in

TB/HIV patients these includes; Cervicitis, Vaginal discharge, Genital ulcers, Inguinal bubo, Gonorrhoea, syphilis, Chancroid, Candidiasis etc.[18] The diagnosis of these HIV – related diseases usually rests on characteristic clinical features such as *Herpes simplex* (oral and genital), *Varicella zooster*, Human papilloma virus, *Molluscum contagiosum*, Other fungal infections (such as *Tinea pedis*, Candidiasis, Cutaneous *Cryptococcus histoplasmosis*)as well as bacterial infections (*Impetigo furunclosis*, *Bacilliary angiomatosis*). [18]

2. Herpes simplex viruses can cause oral herpes (cold sores) or genital herpes. These are fairly common infections, but if you have HIV, the outbreaks can be much more frequent and more severe. They can occur at any CD4 cell count.
3. Malaria is common in the developing world. It is more common and more severe in people with HIV infection.
4. Mycobacterium avium complex (MAC or MAI) is a bacterial infection that can cause recurring fevers, general sick feelings, problems with digestion, and serious weight loss. CD4 cell range: under 75.
5. Pneumocystis pneumonia (PCP) is a fungal infection that can cause a fatal pneumonia. CD4 cell range: under 200. Unfortunately this is still a fairly common OI in people who have not been tested or treated for HIV.
6. Toxoplasmosis (Toxo) is a protozoal infection of the brain. T-cell range: under 100.
7. Tuberculosis (TB) is a bacterial infection that attacks the lungs, and can cause meningitis. CD4 cell range: Everyone with HIV who tests positive for exposure to TB should be treated. Major respiratory OIs is the,Pulmonary TB, as the deadly

interaction of TB and HIV affects millions of people in Nigeria, threatens public health, and stretches the already weak infrastructure of the health sector. TB is the leading cause of morbidity and mortality among People Living with HIV/AIDS while HIV is fuelling the epidemic of TB in Nigeria. Lifetime risk of developing disease in a person with latent TB infection Tuberculosis is a chronic infectious disease caused mainly by *Mycobacterium tuberculosis* (and occasionally by *Mycobacterium bovis* or *Mycobacterium africanum.* [18]

8. Gastro intestinal problems. There are various HIV – related causes of oesophageal inflammations associated with pain on swallowing,*Oesophangial candidiasis* which is the commonest HIV – related case of dysphagia. Other gastro intestinal problems are bacterial infections (Salmonellae, Shigella, *C. jejun*i) and
9. Parasitic OIs (Cryptosporidium, Micosporidia, *G. lamblia*, *E. histolytica*, *C. cayetnensis*).[18]

Intestinal parasites cause significant morbidity and mortality. Diseases caused by Enterobius vermicularis, Giardia lamblia, Ancylostoma duodenale, Necator americanus, and Entamoeba histolytica occur in the United States. E. vermicularis, or pinworm, causes irritation and sleep disturbances. Diagnosis can be made using the "cellophane tape test." Treatment includes mebendazole and household sanitation. Giardia causes nausea, vomiting, malabsorption, diarrhea, and weight loss. Stool ova and parasite studies are diagnostic. Treatment includes metronidazole. Sewage treatment, proper handwashing, and consumption of bottled water can be preventive. A. duodenale and N. americanus are hookworms that cause blood loss, anemia, pica, and wasting. Finding eggs in the feces is diagnostic. Treatments include albendazole, mebendazole, pyrantel pamoate, iron supplementation, and blood transfusion. Preventive

measures include wearing shoes and treating sewage. E. histolytica can cause intestinal ulcerations, bloody diarrhea, weight loss, fever, gastrointestinal obstruction, and peritonitis. Amebas can cause abscesses in the liver that may rupture into the pleural space, peritoneum, or pericardium. Stool and serologic assays, biopsy, barium studies, and liver imaging have diagnostic merit. Therapy includes luminal and tissue amebicides to attack both life-cycle stages. Metronidazole, chloroquine, and aspiration are treatments for liver abscess. Careful sanitation and use of peeled foods and bottled water are preventive.[51]

Intestinal parasites cause significant morbidity and mortality throughout the world, particularly in undeveloped countries and in persons with comorbidities. Intestinal parasites that remain prevalent in the United States include *Enterobius vermicularis, Giardia lamblia, Ancylostoma duodenale, Necator americanus,* and *Entamoeba histolytica*.

Enterobius vermicularis. E. vermicularis, commonly referred to as the pinworm or seatworm, is a nematode, or roundworm, with the largest geographic range of any helminth. It is the most prevalent nematode in the United States. Humans are the only known host, and about 209 million persons worldwide are infected. More than 30 percent of children worldwide are infected. Adult worms are quite small; the males measure 2 to 5 mm, and the females measure 8 to 13 mm. The worms live primarily in the caecum of the large intestine, from which the gravid female migrates at night to lay up to 15,000 eggs on the perineum. The eggs can be spread by the fecal-oral route to the original host and new hosts. Eggs on the host's perineum can spread to other persons in the house, possibly resulting in an entire family becoming infected. [51]

Ingested eggs hatch in the duodenum, and larvae mature during their migration to the large intestine. Fortunately, most eggs desiccate within 72 hours. In the absence of host autoinfection,

infestation usually lasts only four to six weeks. Disease secondary to *E. vermicularis* is relatively innocuous, with egg deposition causing perineal, perianal, and vaginal irritation. The patient's constant itching in an attempt to relieve irritation can lead to potentially debilitating sleep disturbance. Rarely, more serious disease can result, including weight loss, urinary tract infection, and appendicitis. Pinworm infection should be suspected in children who exhibit perianal pruritus and nocturnal restlessness. Direct visualization of the adult worm or microscopic detection of eggs confirms the diagnosis, but only 5 percent of infected persons have eggs in their stool. The "cellophane tape test can serve as a quick way to clinch the diagnosis.[51]

G. lamblia. G. lamblia is a pear-shaped, flagellated protozoan that causes a wide variety of gastrointestinal complaints. Giardia is arguably the most common parasite infection of humans worldwide, and the second most common in the United States after pin-worm. Between 1992 and 1997, the Centers for Disease Control and Prevention (CDC) estimated that more than 2.5 million cases of giardiasis occur annually. Because giardiasis is spread by fecal-oral contamination, the prevalence is higher in populations with poor sanitation, close contact, and oral-anal sexual practices. The disease is commonly water-borne because Giardia is resistant to the chlorine levels in normal tap water and survives well in cold mountain streams. Because giardiasis frequently infects persons who spend a lot of time camping, backpacking, or hunting, it has gained the nicknames of "backpacker's diarrhea" and "beaver fever.[9]

Food-borne transmission is rare but can occur with ingestion of raw or undercooked foods. Giardiasis is a zoonosis, and cross-infectivity among beaver, cattle, dogs, rodents, and bighorn sheep ensures a constant reservoir. The life cycle of Giardia consists of two stages: the fecal-orally transmitted cyst and the disease-causing trophozoite. Cysts are passed in a host's feces,

remaining viable in a moist environment for months. Ingestion of at least 10 to 25 cysts can cause infection in humans. When a new host consumes a cyst, the host's acidic stomach environment stimulates excystation. Each cyst produces two trophozoites. These trophozoites migrate to the duodenum and proximal jejunum, where they attach to the mucosal wall by means of a ventral adhesive disk and replicate by binary fission. Giardia growth in the small intestine is stimulated by bile, carbohydrates, and low oxygen tension. It can cause dyspepsia, mal-absorption, and diarrhea. A recent theory suggests that the symptoms are the result of a brush border enzyme deficiency rather than invasion of the intestinal wall. Some trophozoites transform to cysts and pass in the feces. Clinical presentations of giardiasis vary greatly. After an incubation period of one to two weeks, symptoms of gastrointestinal distress may develop, including nausea, vomiting, malaise, flatulence, cramping, diarrhea, steatorrhea, and weight loss. A history of gradual onset of a mild diarrhea helps differentiate giardiasis or other parasite infections from bacterial etiologies. Symptoms lasting two to four weeks and significant weight loss are key findings that indicate giardiasis. Chronic giardiasis may follow an acute syndrome or present without severe antecedent symptoms. Chronic signs and symptoms such as loose stool, steatorrhea, a 10 to 20 percent loss in weight, malabsorption, malaise, fatigue, and depression may wax and wane over many months if the condition is not treated. Rarely, patients with giardiasis also present with reactive arthritis or asymmetric synovitis, usually of the lower extremities. Rashes and urticaria may be present as part of a hypersensitivity reaction. [51]

Cyst excretion occurs intermittently in both formed and loose stools, while trophozoites are almost only found in diarrhea. Stool studies for ova and parasites (O&P) continue to be a mainstay of diagnosis despite only low to moderate sensitivity. Examination of a single stool specimen has a sensitivity of 50 to 70 percent; the sensitivity increases to 85 to 90 percent with

three serial specimens. Because *Giardia* is not invasive, eosinophilia, and peripheral or fecal leukocytosis do not occur. Antigen assays use enzyme-linked immune sorbent assay (ELISA) or immune fluo-rescence to detect antibodies to trophozoites or cysts. Sensitivities range from 90 to 99 percent, with specificities of 95 to 100 percent compared with stool O&P. Despite the high yield of these studies, direct microscopy is still important, because multiple diarrhea-causing infectious etiologies can be present simultaneously. Duodenal aspirates and biopsies give a higher yield than stool studies but are invasive and usually not necessary for diagnosis. Serology and stool cultures are generally unnecessary. Polymerase chain reaction (PCR) analysis, while only experimental, may be effective for screening water supplies.[9]

A. duodenale and *N. americanus*. Two species of hookworm, *A. duodenale* and *N. americanus*, are found exclusively in humans. *A. duodenale*, or "Old World" *hookworm*, is found in Europe, Africa, China, Japan, India, and the Pacific islands. *N. americanus*, the "New World" hookworm, is found in the Americas and the Caribbean, and has recently been reported in Africa, Asia, and the Pacific. [51]

Until the early 1900s, *N. americanus* infestation was endemic in the southern United States and was only controlled after the widespread use of modern plumbing and footwear. Even though the prevalence of these parasites has drastically decreased in the general population, the CDC reports that in the United States, hookworm infection is the second most common helminthic infection identified in stool studies. *N. americanus* ranges from 10 to 12 mm in length for females and 6 to 8 mm for males. It is distinguished from its slightly larger European cousin by its semilunar dorsal and ventral cutting plates at the buccal cavity compared with *A. duodenale's* two pairs of ventral cutting teeth. The eggs of both worms are 60 to 70 μm in length and bounded by an ovoid

transparent hyaline membrane; they contain two to eight cell divisions. Both species share a common life cycle. Eggs hatch into rhabditiform larvae, feed on bacteria in soil, and molt into the infective filariform larvae. Enabled by moist climates and poor hygiene, filariform larvae enter their hosts through pores, hair follicles, and even intact skin. Maturing larvae travel through the circulation system until they reach alveolar capillaries. Breaking into lung parenchyma, the larvae climb the bronchial tree and are swallowed with secretions. Six weeks after the initial infection, mature worms have attached to the wall of the small intestine to feed, and egg production begins. [51]

The greatest concern from infection is blood loss. Aided by an organic anticoagulant, a hookworm consumes about 0.25 mL of host blood per day. The blood loss caused by hookworms can produce a microcytic hypochromic anemia. Compensatory volume expansion contributes to hypoproteinemia, edema, pica, and wasting. The infection may result in physical and mental retardation in children. Eosinophilia has been noted in 30 to 60 percent of infected patients. While clinical history, hygiene status, and recent travel to endemic areas can give important clues, definitive diagnosis rests on microscopic visualization of eggs in the stool.

E. histolytica. Amebiasis is caused by *E. histolytica*, a protozoan that is 10 to 60 μm in length and moves through the extension of finger-like pseudo-pods. Spreading occurs via the fecal-oral route, usually by poor hygiene during food preparation or by the use of “night soil” (crop fertilization with human waste), as well as by oral-anal sexual practices. Spreading is frequent in persons who have a deficient immune system. Crowding and poor sanitation contribute to its prevalence in Asia, Africa, and Latin America. Approximately 10 percent of the world's population is infected, yet 90 percent of infected persons are asymptomatic. Of the roughly 50

million symptomatic cases occurring each year, up to 100,000 are fatal. The stable reservoir of infective cases complicates eradication. After malaria, it is likely that *E. histolytica* is the world's second leading protozoan cause of death.[9]

Much like Giardia, the two stages in the *E. histolytica* life cycle are cysts and trophozoites. Infective cysts are spheres of about 12 μm in diameter that have one to four nuclei and can be spread via the fecal-oral route by contaminated food and water or oral-anal sexual practices. The pseudopodal trophozoite is about 25 μm across, has a single nucleus, and may contain red blood cells of the host in various stages of digestion. Ingested cysts hatch into trophozoites in the small intestine and continue moving down the digestive tract to the colon. Also like Giardia, some ameba trophozoites become cysts that are passed in the stool and can survive for weeks in a moist environment. However, trophozoites can invade the intestinal mucosa and spread in the bloodstream to the liver, lung, and brain. [51]

Amebiasis can cause both intraluminal and disseminated disease. In the intestinal lumen, *E. histolytica* can disrupt the protective mucus layer overlying the colonic mucosa. The resulting epithelial ulcerations can bleed and cause colitis, usually two to six weeks after initial infection. Acute progression to malaise, weight loss, severe abdominal pain, profuse bloody diarrhea, and fever can occur, often leading to a misdiagnosis of appendicitis, especially in children. In chronic smoldering cases, inflammatory bowel disease can be misdiagnosed, and treatment with steroids only exacerbates the infection. [51]

Tissue penetration and dissemination are possible. Trophozoites that penetrate the intestinal wall spread through the body via the portal circulation. Amebas are chemotactic, attracting neutrophils in the circulation. Amebic liver abscesses form because of toxin release and

hepatocyte damage, and usually develop within five months after infection. Symptoms of a developing abscess include fever, dull pleuritic right upper quadrant pain radiating to the right shoulder, and pleural effusions. Diarrhea is present in only one of three patients with abscess. Fever is the presenting symptom in 10 to 15 percent of patients, and therefore amebic abscess should be considered in patients with a fever of unknown origin. Abscesses may rupture into the pleural space, peritoneum, or pericardium, requiring emergency drainage. Traditional O&P stool testing for amebiasis should use at least three fresh samples to increase sensitivity. However, this test has recently fallen out of favor because an *E. histolytica* stool antigen test with a sensitivity of 87 percent and a specificity of more than 90 percent has become available. Stool culture and PCR testing modalities used in research are not yet sufficiently widespread to be clinically useful. Positive stool samples are likely to be heme positive and to have low neutrophils but may contain Charcot-Leyden crystals, indicating the presence of eosinophils. Biopsy of colonic ulcer edges may yield intramural trophozoites but carries with it the risk of perforation.[5]

Serologic tests such as ELISA and agar gel diffusion are more than 90 percent sensitive, but these tests often become negative within a year of initial infection. Approximately 75 percent of infected patients have leukocytosis, but mucosal invasion does not cause eosinophilia. Liver function tests usually are normal but may show minimal elevation of alkaline phosphatase, even in the presence of large abscesses. To avoid misdiagnosis, patients with suspected ulcerative colitis must be tested for *E. histolytica* antibodies before starting steroid therapy. Intestinal barium studies may be useful in identifying possible amebomas, but biopsy is required to confirm the diagnosis and rule out neoplasia. Liver imaging studies, such as ultra-sonography, computed tomography, magnetic resonance imaging, and nuclear medicine scans, can reveal abscesses as oval or round hypoechoic cysts, usually in the right lobe of the liver. [10]

Risk of complications increases with cysts of more than 10 cm, multiple cysts, superior right lobe involvement, or any left lobe involvement. Repeat studies may be confusing by showing larger abscesses in improving patients. Although two thirds of abscesses resolve within six months, approximately 10 percent of abscesses persist for more than a year.[11]

2.3.2 Driving forces of HIV/OIs epidemic.

These include Ignorance, denial, misconceptions. Promiscuity, Prostitution, STDs**,** Poverty, Rural/urban drift**,** Cultural beliefs, biases in favour of males**,** Lack of political will/commitment**,** Misplacement of national priority**,** Poor health resource setting (inadequate facilities, staff, drugs, etc**),** Stigma and discrimination[17]

2.4 Public-health approach to antiretroviral treatment against HIV/opportunistic infections in resource-limited settings

WHO has proposed a public-health approach to antiretroviral therapy (ART) to enable scaling-up access to treatment for HIV-positive people in developing countries, recognizing that the western model of specialist physician management and advanced laboratory monitoring is not feasible in resource-poor settings. In this approach, standardized simplified treatment protocols and decentralized service delivery enable treatment to be delivered to large numbers of HIV-positive adults and children through the public and private sector. Simplified tools and approaches to clinical decision-making, centered on the "four Ss"—when to: start drug treatment; substitute for toxicity; switch after treatment failure; and stop—enable lower level health-care workers to deliver care.[18]

Simple limited formularies have driven large-scale production of fixed-dose combinations for first-line treatment for adults and lowered prices, but to ensure access to ART in the poorest

countries, the care and drugs should be given free at point of service delivery. Population-based surveillance for acquired and transmitted resistance is needed to address concerns that switching regimens on the basis of clinical criteria for failure alone could lead to widespread emergence of drug-resistant virus strains. The integrated management of adult or childhood illness (IMAI/IMCI) facilitates decentralized implementation that is integrated within existing health systems. Simplified operational guidelines, tools, and training materials enable clinical teams in primary-care and second-level facilities to deliver HIV prevention, HIV care, and ART, and to use a standardized patient-tracking system.[18,19]

Sequential ART regimens.2 International consensus on a management is fragile. This difficulty in translating simple first-line antiretroviral combination for adults guidelines from developed to developing nations caused meant that production and supply of ARTs could be concerns over whether ART scale-up in poor countries was scaled-up. Once fixed-dose combinations became widely feasible, let alone affordable or cost-effective. Available, and prices had fallen substantially, the WHO Drawing on experience from using the DOTS approach announced its 3 by 5 initiative (to strive for 3 million for tuberculosis. The World Health Organization (WHO) began approach on antiretroviral to develop people in low-income and middle-income countries towards improving public-health approach in ART services by 2005).[19].

Although the initiative did took into account country requirements, the realities of not meet its target, by the end of 2005, around 1·3 million weak health systems, and the experiences of pioneering people were receiving WHO-recommended first-line ART programmes. The key tenets were standardization regimens compared with 400 000 in 2003. A recent and

simplification of regimens to support efficient assessment noted that almost all focus countries for ART implementation, ensuring ART programmes were based scale-up had either adapted or used on the most rigorous scientific data and equity—aiming recommendations to shape national policy. Treatment to set standards for treatment that should be accessible programmes and centers report good initial responses by all in need. The key conceptual shift was the move. Despite these achievements, there remains considerable from an individual-based approach to a population-based uncertainty about what should constitute a public-health one, recognised as the only way to make ART rapidly approach to ART.[20]

2.4.1 ART regimens

Around 40 million people worldwide are thought to be infected with HIV. Many of these people live in developing countries. Since 2001, the WHO has been promoting a public-health approach to antiretroviral therapy (ART) to improve access in resource-poor settings. Existing guidelines for ART and the prevention of mother to child transmission were revised earlier this year, and separate guidelines for treating children were developed. Other publications support the public-health approach to ART delivery and free and equitable access to ART. The integrated Management of Adult Adolescent, and Childhood Illness (IMAI/IMCI) has been developed to support decentralized implementation in resource-poor countries. Treatment options have been consolidated into two sequential ART regimens. International consensus on a simple first-line antiretroviral combination for adults meant that production and supply of ARTs could be scaled-up.[19]

Once fixed-dose combinations became widely available, and prices had fallen substantially, the WHO announced its 3 by 5 initiative (to strive for 3 million people in low-income and middle-income countries to be on antiretroviral by 2005). Although the initiative did not meet its target, by the end of 2005, around 1·3 million people were receiving WHO-recommended first-line regimens compared with 400 000 in 2003. A recent assessment noted that almost all focus countries for ART scale-up had either adapted or used WHO recommendations to shape national policy;15 treatment programmes and centers report good initial responses.16,17 Despite these achievements, there remains considerable uncertainty about what should constitute a public-health approach to ART. We summarize here the WHO's approach, and clarify its importance for treatment providers, HIV programme managers, and policymakers in developing countries.[20]

2.4.2 Recommended first and second-line ART regimens

AZT=zidovudine. d4T=stavudine. 3TC=lamivudine. FTC=emtricitabine.TDF=tenofovir. ABC=abacavir. EFV=efavirenz. NVP=nevirapine. *Not used for children younger than 13 years.†Not recommended for children younger than 3 years or weighing less than 10 kg. ‡PI choices are more limited in children. §Optional. The triple NRTI approach can be used to avoid NNRTI drug-drug interactions and toxicity. AZT and 3TC could be used "strategically"; AZT can prevent or delay the emergence of the K65R mutation, and 3TC can maintain the M184V mutation that could reduce the virus' ability to replicate as well as induce some viral resensitisation to AZT. [18,19,20]

2.4.3 standardised regimens and simplified formularies

The first, arguably most important, achievement has been to standardise first-line and second-line treatments. There are three classes of oral antiretrovirals available: nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTI and NNRTI) and protease inhibitors (PI).

Public-health therapy readily accommodates the use of two sequential triple-drug ART regimens. On the basis of available data, the initial consensus was to use one NNRTI in first-line treatment, supported by an NRTI;2 this remains in the 2006 recommendations.4–6 PIs are reserved for second-line therapy, supported by an NRTI using two new (previously unused) agents to minimise cross-resistance. Second-line potency depends on the PI class, and any initial treatment that includes a PI uses a class preserved for second line therapy, and makes efforts to construct a potent second line regimen impossible.[20]

To derive a simplified antiretroviral formulary and make ART scale-up feasible, it has proven necessary to be prescriptive about first-line and second-line treatment. There is less experience with, and demand for, second-line ART for adults. With limited use and simple formulations not yet developed, the market has not yet responded in the same way it did for first-line therapy: one fixed-dose combination is produced; prices remain high; and countries are not widely procuring second-line antiretrovirals. Similar constraints have restricted the availability of first-line and second-line treatments for children; only three fixed-dose combinations are available from two manufacturers. [18,19]

With a standard first-line and second-line sequence of therapy established, patient management can centre on the "four Ss" of simplified clinical decision-making, when to: start; substitute for toxicity; switch treatment after failure; and stop, moving to end-of-life care. This is supported by regular clinical assessment: revised guidelines for staging HIV disease describe four stages for both adults and children (paediatric staging was confusingly three-tiered1) and are used to identify when to start ART.8 Previously staging was hierarchical and irreversible; with immune

reconstitution and improvement of clinical status, a new concept of staging on therapy (T-staging) to inform when to switch treatment is being developed. Although treatment decisions can be made with clinical information alone, it is better informed with immunological (CD4-cell) monitoring. The WHO has outlined immunological classification of established HIV infection and is now advocating for much wider access to CD4-monitoring technology.[20]

Viral load monitoring, although desirable, is not currently regarded as essential for patient management within a public-health approach. To some extent this is pragmatic because of the procedure's high cost and technical complexity. A more fundamental reason is the utility of viral load measurement. Defining failure of first-line therapy as any detectable or "low" values in asymptomatic or stable patients could precipitate premature switching of ART regimens with potential loss of subsequent years' benefit from a first-line regimen. Such monitoring is informative as to when to switch regimens only if multiple subsequent individually tailored regimens are feasible. When cohort studies can identify threshold levels that define first-line failure; and simpler technology, ideally point-of-care, to monitor viral load can be developed and marketed, such monitoring may have value for a public-health approach. The WHO advocates for wider access to viral-load monitoring in specialist centres for management of complex cases,4–6 and for virological diagnostic purposes for infants, including using dry blood-spots.[20]

2.5 General characteristics of Cryptosporidium

Cryptosporidium is a protozoan of the phylum *Apicomplexa* and causes a diarrhoeal illness called Cryptosporidiosis. Other *Apicomplexan* pathogens include the malaria parasite *Plosmodium,* and *Toxoplosma,* the causative agent of toxoplasmosis. Unlike plasmodium, which transmits via a mosquito vector, *Cryptosporidium* does not utilize an insect vector and is capable

of completing its life cycle within a single host, resulting in microbial cyst stages which are excreted in feces and are capable of transmission to a new host. A number of *Cryptosporidium* infect mammals. In humans, the main cause.s of disease are *C. parvum* and *C. hominis* (previously *C. parvum* genotype I). *C. canis, C. felis, C. meleagridis,* and C. *muris* can also cause disease in humans. *Cryptosporidium*, is typically an acute short-term infection but can become severe and non-resolving in children and immuno compromised individuals. In humans, it remains in the lower intestine and may remain for up to five weeks. The parasite is transmitted by environmentally microbial cysts (oocysts) that, once injected, excyst in the small intestine and result in an infection of intestinal epithelial tissue[18].

The genomes of *Cryptosporidium parvum* was sequenced in 2004 and was found to be unusual amongst Eukaryotes in that the mitochondria seem not contain DNA[4]. A closely related species, C, *homimis,* also has its genome sequence available (Ping *et al,* 2004). Thus far eight chromosomes of *Cryptosporidium* have been sequenced, ranging in size from 900-13000kb. As this is an emerging pathogen, projects are currently, underway to better understand the parasitic species genetics and relationship to each other.[8]

2.6 Life cycle of Cryptosporidium species

The life cycle of *Cryptosporidium parvum* consists of an asexual stage and a sexual stage[8]. After being ingested, the oocysts excyst in the small intestine. They release Sporozoites that attach to the microvilli of the epithelial cells of the small intestine. From there they become trophozoites that reproduce asexually by multiple fission, a process known as Schizogony. The trophozoites develop into type I metrons that contain 8 daughter cells. These daughter cells are Type I merozoites, which get released by the metrons which get released by the meronts. Some of these

merozoites can cause auto infection by attaching to epithelial cells[21]. Other of these merozoites become Type II merons which contain 4 Type II merozoites (Ryan *et al,* 2004). These merozoites get released and they attach to the epithelial cells. From there they become either macrogamonts or microgamonts[18]. These are the female and male sexual forms, respectively[19]. This stage, when sexual forms arise, is called gametogony[22]. Zygotes are formed by microgamates from the microgament penetrating the macrogamonts. The zygotes develop into oocysts of two types[19]. Twenty percent (20%) of oocysts have thin walls and so can re infect the host by rupturing and releasing sporozoite that start the process over again[17]. The thick-walled oocysts are excreted into the environment[19]. The oocysts are matured and infective upon being excreted[17]. They can also resist many common disinfectants, notably chlorine-based disinfectants.[23,24]

2.7 Pathogenesis

Crypto can cause severe illness for a long time in people infected with HIV. You can die from crypto. If your CD4 cell count is below 200, crypto may give you symptoms for a long time. If your CD4 cell count is above 200, your symptoms may last only 1 to 3 weeks. But even after your symptoms go away, you may still be carrying crypto. If you are carrying crypto, even without symptoms, you can give it to someone else. Also, your own symptoms may come back if your CD4 cell count later drops below 200[24].

The oocysts are ovoid or sphercial and measure 5 to 6 micrometers across. When in flotation preparations they appear highly retractile. The Oocysts contains up to 4 sporozoites that are bow-shaped[8]. As few as 2 to 10 Oocysts can initiate an infection[19]. The parasite is located in the brush border of the epithelial cells of the small intestine[24]. They are mainly located in the

jejunum. When the sporozoites attach the epithelial cells' membrane envelops them. Thus, they are "intracellular but extracytoplasmic[23]. The infected human excretes the most Oocysts during the first week[8]. Oocysts can be execrated for weeks after the diarrhoea subsides[24]. The immune system reduces the formation of Type l metrozoites as well as the number of thin-walled oocysts[17]. This helps prevent auto-infection. B cells do not help with the initial response or the fight to eliminate the parasite[19].

2.8 Epidemiology of Cryptosporidiosis

The use of epidemiology techniques (study of disease occurrence and distribution) has helped in solving the mysteries of diseases that spread rapidly among human population with devastating effects. Moreover, epidemiological studies have had practical benefits by leading to an understanding of how to control the spread the infections disease[25]. Cryptosporidiosis is found worldwide. It causes 50.8% of water-borne diseases that are attributed to parasites[26]. In developing countries 8-19% of diarrhoea diseases can be attributed to *Cryptosporidium*[27]. Ten percent (10%) of the population in developing countries excretes Oocysts. In developing countries the number is lower at 1-3%. The age group most affected is children from 1-9 years old[19]. The following groups have an elevated risk of being exposed to *Cryptosporidium*[10]

- People who swim regularly in pools with insufficient sanitation (certain strains of *Cryptosporidium* are chlorine resistant).
- Child care workers
- Parents of infected children
- People who take of other people with *Cryptosporidiosis*
- International travelers

- Backpackers, hikers and campers who drink unfiltered, untreated water.
- People, including swimmers, who swallow water from contaminated sources.
- People who handle infected cattle
- People exposed to human feces through sexual contact.

Cases of *Cryptosporidiosis* can occur in a city the does not have a contaminated water supply. In a city with clean water, it may be that cases of *Cryptosporidiosis* have different origins. Testing of water, as well as epidemiological study, is necessary to determine the sources of specific infections. Note that *Cryptosporidiosis* typically does not cause serious illness in healthy people. It may chronically sicken some children, as well as adults who are exposed and immuno compromised. A subset of the immuno compromise population is people with AIDS. Some sexual behaviour can transmit the parasite directly[10].

2.9 Transmission of Cryptospor1dium infection

Crypto is spread by having contact with faeces containing crypto. Crypto is not spread by contact with blood. You can get crypto by putting anything in your mouth that has touched the feces of a person or animal infected with crypto. You can't tell by looking whether something has been in contact with feces, so you need to be aware of what these things may be. Things likely to be contaminated with feces are[28]:

- skin around a person's anus
- skin or fur of farm animals and household pets
- cat litter boxes
- children in diapers
- clothing, bedding, toilets, or bed pans used by someone with diarrhea

- dirt in gardens, sand boxes, yards, parks, etc. where animals may have had bowel movements
- uncooked or unwashed food
- Water for bathing, swimming, or drinking especial when traveling abroad[28].

Infection is though contaminated material such as earth, water, uncooked or cross-contaminated food that has been in contact with the feces of an infected individual or animal. Contact must then be transferred to the mouth and swallowed. It is especially prevalent amongst those in regular contact with bodies in fresh water including recreational water such as swimming pools. Other potential sources include insufficiently treated water supplies, contaminated food, or exposure to faeces[10]. The high resistance of *Cryptosporidium* oocysts to disinfectants such as chlorine bleach enables them to survive for long periods and still remain infective[29]. Some outbreaks have happened in day care related to diaper changes[10].

2.10 Clinical symptoms of Cryptosporidiosis

Symptoms appear from two to ten days after infection, with an average of 7days and last for up to two weeks, or in some cases up to one month[10]. There are 3 possible forms of the illness in immune competent people. The disease can be asymptomatic or cause acute diarrhoea or persistent diarrhoea that can last for a few weeks. Diarrhoea is usually watery with mucus. It is very rare to find blood or lenkocytes in the diarrhoea, as well as watery diarrhoea, there are often stomach pains or cramps and a low fever[19]. Other symptoms include nausea, vomiting watery diarrhea, stomach cramps, an upset stomach, low grade fever, weight loss from severe diarrhea[29]. Malabsorption[23], and dehydration[30]. Anorexia can occur as can weight loss[17]. Individuals who are asymptomatic (have no symptoms) are nevertheless infective, and thus can pass on the

infection to others. Even after symptoms have finally subsided an individual is still infective for some weeks. Severe disease, including pancreatitis, cans occur[31].

Immune compromised people as well as very young or very old people, can develop a more severe form of cryptosporidiosis[24]. There are 4 clinical presentations for patients with AIDS. 4% have no symptoms, 29% have a transient infection, 60% have chronic diarrhoea, and 8% have a severe, cholera-Like infection. With transient infections diarrhoea ends within 2months and *Cryptosporidium* is no longer found in feces. Chronic diarrhoea is diarrhoea that lasts for 2 or more months. The most severe form results in the patients excreting at least 2 litres of watery diarrhoea per day[19]. They can lose up to 25 liters per day[17]. AIDS patients can have up to 10 stools per day. They experience severe mal-absorption and can have 10% weight loss. Many of them never completely eliminate *Cryptosporidium* from their bodies[19].

When *Cryptosporidium* spreads beyond the intestine as it can predominantly in patients with AIDS, it can reach the lungs, middle ear, pancreas and stomach. Thus, one symptom is pain in the right upper quadrant [23]. The parasite can infect the biliary tract, causing biliary Cryptosporidiosis. This can result in cholecystitis and cholangitis[17].

2.11 Management and treatment of opportunistic infections

There are many diagnostic tests for *Cryptosporidium.* They include microscopy, staining, and detection of antibodies. Microscopy can help identify oocysts in fecal matter[24]. To increase the chance of finding the oocysts the diagnostician should inspect at least 3 stool samples. There are several techniques to concentrate either the stool sample or the oocysts. The modified Formalin-ethyl acetate (FEA) concentration method concentrates the stool[23]. Both the modified zinc sulfate

centrifugal flotation techniques and the sheather's sugar flotation procedure can concentrate the oocysts by causing them to float[20]. Another form of microscopy is florescent microscopy done by staining with auramine[24].

Other staining techniques include acid-fast staining[19] which will stain the Oocysts red[23]. One type of acid-fast stain is the Kinyoun technique[26]. Giemsa staining can also be performed[17]. Part of the small intestine can be stained with hematoxylin and eosin (H&E), which will show Oocysts attached to the epithelial cells[23].

Detection of antigens is yet another way to diagnose the disease. This can be done with direct florescent antibody[9]. It can also be achieved through indirect immuno florescent assay[20]. Enzyme-Linked Immuno Sorbent Assay (ELISA) also detects antigens[24].

Polymerase Chain Reaction (PCR) is another way to diagnose Cryptosporidiosis. It can even identify the specific species of *Cryptosporidium*[9]. If the patient is thought to have biliary Cryptosporidiosis then an appropriate diagnostic technique is ultra sonography. If that returns normal results the next step would be to perform endoscopic retrograde cholangiopencreatography.[24]

2.11.1 Management of Diarrhea in HIV Disease

When evaluation of diarrhea reveals an enteric pathogen, specific therapy should be administered if available. Chronic administration of alternating antibiotics may be necessary for recurrent *Salmonella*, *Shigella*, *Campylobacter*, or *Isospora* infections. An empiric trial of oral antibiotics

or antiparasite therapy for the possibility of small bowel overgrowth, undetected *Campylobacter*, *Isospora* enteritis, or undetected protozoa can be considered. Sulfonamides, ciprofloxacin, tetracyclines, or metronidazole may be appropriate in this setting.[25]

HIV-infected patients with chronic diarrhea should be treated symptomatically. Antidiarrheals, including Imodium, Lomotil, or tincture of opium drops, are often required and should be titrated individually. Lactose-containing foods should be avoided as a diagnostic and therapeutic trial. Bulk-forming agents, including effersyllium, bran, and pectin may be helpful. Nutritional repletion will increase the patient's sense of well-being, although a survival benefit has not been demonstrated. In cases of severe diarrhea, short- or long-term intravenous fluid repletion may be indicated. [26]

Numerous agents have been tested in patients with HIV-associated diarrhea, and controlled studies have failed to define a definitive treatment for cryptosporidiosis, microsporidiosis or pathogen-negative diarrhea. Promising new data indicate that microsporidiosis and cryptosporidiosis infection may be cleared in patients receiving highly effective antiretroviral therapy. The changing clinical diagnosis witnessed in the era of antiretroviral therapy has limited research on anti-infective agents. One recent study of the effects of an extract from a tropical plant showed promising declines in stool weight over 4 days of treatment in patients with AIDS and virtually no pathogens. [17]

The somatostatin analogue octreotide (administered subcutaneously) appears to be particularly effective in patients with diarrhea who lack a specific infection. This agent's putative mechanism of action is via inhibition of a broad array of GI hormones that regulate intestinal fluid and

electrolyte secretion. As a result of its inhibition of cholecystokinin, gallbladder ileus with stone formation and increased fat malabsorption may occur.[18]

2.11.1.1 Weight loss

Involuntary weight loss is a common condition associated with advancing HIV disease and gastrointestinal symptoms. The CDC classifies wasting as an AIDS diagnosis when a patient presents with involuntary weight loss of more than 10% of baseline body weight, plus either chronic diarrhea or chronic weakness and fever in the absence of infection or a condition other than HIV disease. Wasting syndrome accounted for 20% of AIDS-defining diagnoses in 1995. In the setting of progressive weight loss, death is inevitable once body weight falls below roughly 66% of ideal body weight. Weight loss above 5 to 10% from usual weight predicts mortality, independent of CD4 count. Body cell mass (BCM), the metabolically active body component, is an earlier and more specific predictor of mortality[20].

Involuntary weight loss can be classified into two different etiologies, caloric deficit and metabolic disturbance. Inadequate caloric intake and weight loss may be due to upper intestinal abnormalities (anorexia, nausea, vomiting), psychosocial and economic factors, fatigue, mental status changes, and medications. Patients frequently reduce their oral intake to decrease symptoms of diarrhea or abdominal pain. Caloric deficit results in a selective utilization of body fat stores for energy, an adaptive process to preserve lean body mass (starvation model). In contrast, metabolic derangements leading to increased energy expenditure or abnormal energy substrate utilization due to opportunistic infection (or other disease state) result in a disproportionate loss of lean body mass with relative preservation of body fat stores[21]

Caloric deficit is one cause of weight loss that may be due to odynophagia, dysphagia, anorexia, altered sense of taste, early satiety, nausea, vomiting, diarrhea, fever, fatigue, apathy and/or depression. Pharmacologic side effects, opportunistic infections that result in lesions in the mouth or esophagus, and malabsorption of nutrients can be the underlying causes of reported symptoms. Self-restriction of caloric intake to reduce diarrhea, nausea, and vomiting is also common among patients[19]

Abnormal resting energy expenditure (REE) has also been associated with abnormal weight loss. Grunfeld and associates found REE to be increased compared to controls by 11% in patients who were HIV positive, 25% in patients with AIDS, and 29% in patients with AIDS who had a secondary infection. Over the course of the 28-day study, patients in the control, HIV-positive, and AIDS group each maintained caloric intake, while patients with AIDS and a secondary infection had a decreased caloric intake of 36% and a 5% weight loss[20]

While REE increases throughout the course of disease, Macallan et al. reported that decreases in caloric intake and total energy expenditure (TEE) are the primary determinants of weight loss. These investigators completed 51 assessments of energy metabolism on 27 men with HIV infection at different stages of their disease: rapid weight loss, slow weight loss, stable weight, or weight gain. In addition to finding an increased REE in all groups, the determinant of weight loss patterns was clearly caloric deficit and TEE. The rapid weight loss group had an average deficit of 800 kcals, whereas the weight gain group was 400 kcals above energy expenditure[22]

Macallan and associates have also recognized weight loss to be either rapid or slow in patients with stage IV HIV disease. In a study of 30 men, serial weight measurements were followed closely. An association was found between acute weight loss episodes and opportunistic

infections, with weight loss preceding the infection; caloric deficit and increased REE was also noted. Patients who were found to have chronic weight loss had associated gastrointestinal disease; 68% of these patients had documented malabsorption. Weight regain without nutrition support is not uncommon in patients with acute weight loss, especially after the resolution of an infection. Patients with chronic weight loss can regain weight, however, but most likely will require liquid nutrition supplements long-term.[22]

2.11.1.2 Evaluation of Weight Loss

All patients infected with HIV should have a regular nutritional and functional assessment. Weight loss, body composition changes, and exercise/functional limitations are indicators of advancing disease that may be reversible. All patients who have lost weight should have a thorough evaluation for symptoms contributing to inadequate intake and interventions to promote weight gain should be initiated promptly. The clinical assessment should identify markers and predictors of malnutrition. A careful review of symptoms will identify barriers to adequate oral intake: anorexia, early satiety, dysgeusia, nausea, vomiting, weakness/fatigue, odynophagia, dysphagia, poor dentition, diarrhea, and abdominal pain. In addition, conditions that increase energy requirements should also be noted, including: fever, tachypnea, systemic infections, increased physical activity. [22]

A detailed review of medications and "alternative therapies" (including herbal therapy and megadosing of vitamins and minerals) may provide insight into potential side-effects. A social history is also important to identify environmental or financial obstacles to obtaining, storing, and preparing food.[22]

2.11.1.3 Treatment of Weight Loss

The goal of nutrition therapy is to preserve lean body mass. Routine evaluations by a registered dietitian who can monitor changes in weight, body composition (body cell mass), caloric intake, and activity levels are extremely useful to prevent weight loss and malnutrition. Based on the evaluation of the patient, estimated caloric intake should be determined and 3-day food records should be administered to review patients actual intake. While guidelines for carbohydrate and fat have not been established, protein requirements should be at least 1.0 to 1.2 g/kg in the absence of secondary infection. Nutrient intake should be at least 100% of the Recommended Dietary Allowance; a multivitamin is commonly suggested for patients with HIV to ensure these requirements are met.[21]

Appetite stimulants are often effective in treating anorexia, a major cause of involuntary weight loss. Dronabinol (Marinol), a synthetic derivative of marijuana, and Megastrol acetate (Megace), a synthetic progestational drug, have been associated with increased appetite and weight. In addition to its effects as an appetite stimulant, Marinol may also improve mood and decrease nausea. Diarrhea associated with malabsorption requires careful nutrition management. A balance must be found between controlling symptoms with a low-fat diet and maintaining caloric intake with fat-containing foods that offer caloric density. Patients with diarrhea unable to meet caloric requirements may benefit from a liquid nutrition supplement containing medium-chain triglycerides. Dietary or supplemental soluble fiber may help bind water and improve diarrhea.[24]

If nonvolitional weight loss cannot be reduced or reversed by oral intake and oral liquid nutritional supplements, enteral alimentation should be initiated. Unless otherwise indicated, the gastrointestinal tract should be used for nutrient absorption. Kotler et al. found that patients fed

by endoscopically placed gastrostomy were able to replete body cell mass, but only if the underlying illness is treated concurrently. Percutaneous endoscopic gastrostomy (PEG) feeding tubes are also effective in settings of severe weight loss. Parenteral nutrition should be reserved for severe intestinal dysfunction, such as large volume secretory diarrhea. A clinical trial that randomized participants to total parenteral nutrition (TPN) or nutrition counseling resulted in increased weight and body cell mass in patients who received TPN, however, rehospitalization and survival were the same in both groups.[21]

2.11.2 Treatment of Cryptosporidiosis

For each OI, there are specific drugs, or combinations of drugs, that seem to work best. Refer to the Fact Sheets for each OI to learn more about how they are treated. Strong antiretroviral drugs can allow a damaged immune system to recover and do a better job of fighting OIs. There is not reliable treatment for *Cryptosporidium* enteritis; certain agents such as paromomycin, atovaquone, nitazoxanide[21] and azithromycin are sometimes used, but they usually have only temporary effects[24]. Treatment is primarily supportive. Fluids need to be replaced orally. A lactose-free diet should be taken as tolerated. In rare situations, intravenous fluids may be required. Antibiotics are not usually helpful, and are primarily reserved for persons with severe diseases and a weak immune system sometimes relapses happen[9]. In the immune-competent, majority of such individuals suffer a short (less than 2 weeks) self-limiting course that requires supportive care with re-hydration and occasionally anti-diarrhoeal medication and ends with spontaneous recovery. Nitazoxanide is one drug that US FDA has approved for use in immuno competent to combat diarrhoea[19]. Spiramycin can help shorten the amount of time Oocysts are passed as well as the duration of diarrhoea in children[24].

Similarly, immuno compromised individual such as AIDS patients, cryptosporidiosis resolves slowly or not at all, and frequently causes a particularly severe and permanent form of watery diarrhoea couple with a greatly decreased ability to absorb key nutrients through the intestinal tract. The result is progressively severe dehydration, electrolyte imbalances, malnutrition, wasting, and eventual death. Spiramycin can help treat diarrhoea in patients who are in the early stages of AIDS[35]. The mortality rate for infected AIDS patients is generally based on CD4 + marker counts; patients with CD4 + counts over 180 cells/mm^3 generally recover with supportive hospital care and medication, but in patients with CD4 + counts below 50 cells/mm^3 and 36% of those with counts between 50 and 200 cells/mm^3 died within the first year of contracting the infection (Gilson *et at.*, 1996). In one AIDS patient from Iran, who had pulmonary Cryptosporidiosis in addition to intestinal Cryptosporidiosis, azithromycin and paromomycin helped to clear the infection.[20,25].

Currently, the best approach is to improve the immune status in immune status in immuno deficient individuals. The probiotic Saccharomyces boulardii sold over the counter in pharmacies and health shops has been found to be a helpful natural treatment in managing diarrhoea of various infections origins including *Cryptosporidium*[34]. Parental octreotide acetate can help decrease the number of stools passed[17]. A treatment for patients with biliary Cryptosporidiosis who have cholangitis in addition to papillary stenosis is endoscope sphincterotomy[19].

On the other hand, research is being done in molecular based immuno therapy. For example, synthetic isoflavone derivates have been shown to fight off *Cryptosporidium parvum* in vitro and

in a gerbil. Derivate of nitazoxanide, which are synthetic nitro-or non nitro-thiazolide compounds, have also shown promising results in vitro treatment of drinking water[26]. Many treatment plants that take raw water from rivers, lakes, and reservoirs for public drinking water production use conventional filtration technologies. This involves a series of processes including coagulation, flocculation, sedimentation and filtration. Direct filtration, which is typically used to treat water with low partiicles levels involving slow sand filters, diatomaceous earth filter and membranes will remove 99% of *Cryptosporidium*[1] Membranes and bag and cartridge filters remove *Cryptosporidium* product – Specifically.[27,28,29].

While *Cryptosporidium* is highly resistant to chlorine disinfection[2], with high enough concentrations and contact time *Cryptosporidium* will be inactivated by chlorine dioxide and ozone treatment.[30] The required levels of chlorine generally preclude the use of chlorine disinfection as a reliable method to control *Cryptosporidium* in drinking water. Ultraviolet light treatment at relatively low doses will inactivate *Cryptosporidium.* Water Research Foundation - funded research originally discovered UV's efficacy in inactivating *Cryptosporidium*. The most reliable way to decontaminate drinking water which may be contaminated by *Cryptosporidium* is to boil it[31].

2.12 Prevention and Control of Cryptosporidiosis

Most of the germs that cause OIs are quite common, and you may already be carrying several of these infections. You can reduce the risk of new infections by keeping clean and avoiding known sources of the germs that cause OIs. Even if you’re infected with some OIs, you can take medications that will prevent the development of active disease. This is called prophylaxis. The best way to prevent OIs is to take strong ART. As *Cryptosporidium* is primarily contracted

through drinking water, the prevention and control of this parasite has become a public health concern. Various government committees and associations are at work to regulate the decontamination of born public and private water sources. Prevention methods include the installation of more advanced filtration systems, constant testing of water supply, and educating populations about the signs of the disease and ways to prevent it.[32,33,34].

In the US the law requires doctors and labs to report cases of *Cryptosporidiosis* to local or state health departments. These departments then report to the Center for Diseases Control and Prevention. The best way to prevent getting and spreading *Cryptosporidiosis* is to have good hygiene and sanitation[35], as example would be hand-washing[19]. Prevention is through washing hands carefully after going to the bathroom or contacting stool, and before eating. People should avoid contact with animal feces[36]. They should also avoid possibly contaminated food and water[19]. Additionally people should refrain from engaging in sexual activities that can expose them to feces[37].

Standard water filtration may not be enough to eliminate *Cryptosporidium;* boiling for at least 1 minutes (3 minutes above 6,500 feet (2,000m) of altitude) will decontaminate it. Heating milk at 71.7°c for 15 seconds pasteurizes it and can destroy the oocysts ability to infect[38,39..] Water can also be made safe by filtering with a filter with pore size not greater than 1 micrometre, or by filters that have been approved for "Cyst removal" by the US National Science Foundation NSF[19]. Bottled drinking water is less likely to contain *Cryptosporidium,* especially if the water is from an underground source[40,41].

People who have Cryptosporidiosis should not swim in communal area because *Cryptosporidium* can reside in the anal and genital areas and be washed off. They should wait until at least two weeks after diarrhoea stops before entering public water sources since oocysts can still be shed for a while. Also, they should stay away from immune suppressed people[42]. Immuno compromised people should take care to protect themselves from water in lakes and streams. [43]. They should also stay away from animal stools and wash their hands after touching animals. To be safe they should boil or fitter their water. They should also wash and cook their vegetables[44]. Sources of bottled water (e.g., wells, springs, municipal tap-water supplies, rivers, and lakes) and methods for its disinfection differ; therefore, all brands should not be presumed to be cryptosporidial oocyst-free. Water from wells and springs is much less likely to be contaminated by oocysts than water from rivers or lakes. Treatment of bottled water by distillation or reverse osmosis ensures oocyst removal. Water passed through an absolute 1-µm filter or a filter labeled as meeting NSF Standard No. 53 for cyst removal before bottling will provide approximately the same level of protection. Using nominal 1-µm filters by bottlers as the only barrier to Cryptosporidium might not result in the removal of 99% of Oocysts

2.12.1 Fighting diarrheal diseases in developing countries

The Millennium Development Goals call for reducing by half the proportion of people without sustainable access to safe drinking water.[43,44]. This goal was adopted in large part because clean water was seen as critical to fighting diarrheal disease, which kills 2 million children annually. There is compelling evidence that provision of piped water and sanitation can substantially reduce child mortality.[46] However, in dispersed rural settlements, providing complete piped water and sanitation infrastructure to households is expensive[47]. Many poor countries have therefore focused instead on providing community-level water infrastructure, such as wells.

Various traditional child health interventions have been shown to be effective in fighting diarrhea.[48]

Among environmental interventions, hand washing and point-of-use water treatment both reduce diarrhea, although more needs to be learned about ways to encourage households to take up these behavior changes. In contrast, there is little evidence that providing community-level rural water infrastructure substantially reduces diarrheal disease or that this infrastructure can be effectively maintained. Investments in communal water infrastructure short of piped water may serve other needs, and may reduce diarrhea in particular circumstances, but the case for prioritizing communal infrastructure provision needs to be made rather than assumed.[49,50,51]

The 2008 WHO document on essential interventions for people living with HIV (PLHIV) states that the "lack of safe water exposes people with HIV to increased risk of transmission of waterborne and other enteric pathogens.[20,21,52] Safe drinking-water is essential because water is used to consume medications, prepare food, and ensure adequate hydration Opportunistic infections from contaminated drinking-water can reduce quality of life and be fatal among PLHIV. For example, microbial infections (such as those from *cryptosporidium* and *giardia*) that may be self-limiting in people with a healthy immune response are frequently fatal among PLHIV. In fact, diarrhoea can be a leading cause of death, contributing to as much as 55% of mortality in PLHIV in sub-Saharan Africa. Low-cost and effective HWTS can significantly reduce the pathogen load in drinking-water and, thereby reduce the risk of diarrhoeal diseases and other waterborne illness, underscoring the needs for its integration in HIV prevention and care policies and programmes.[10,11,53]

There are four main types of household water treatment. The Physical removal of pathogens (filtration, adsorption, and/or sedimentation); Chemically treating water to kill or deactivate pathogens, most commonly with chlorine; Disinfection by heat (boiling or pasteurization) and ultraviolet radiation (using the sun or an artificial lamp); and Combination approaches (filtration or flocculation combined with disinfection.)[1,54].

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1 Study area

The study was conducted at Specialist Hospital Sokoto, which is the largest Hospital owned by the Sokoto State Ministry of Health. HIV/AIDS patients visit the Comprehensive HIV/AIDS Services Center established by the Global HIV/AIDS initiative Nigeria (GHAIN), Sokoto Zone as part of an ongoing prospective cohort study. The hospital serves a large number of HIV/AIDS patients from within and outside the metropolis including referred patients from other Health Facilities, NGOs, other related agencies, and Organizations within the state and neighboring states of Kebbi, Zamfara and perhaps voluntary visitors from the neighboring Niger Republic. Sokoto State is located between the longitude $11^{0}30$ and $13^{0}30$ East and Latitude 4^{0} and 6^{0} North. The state is in semi-arid area of Nigeria. It has a tropical climate with a temperature of 38^{o}C-42^{o}C from March-May. Rainfall is scanty and starts late in April and ends early in September, with a mean range of 500-1300mm[32]. The State is one of the leading producers of livestock in the country[34].

3.2 Study design

The study design used for this research on cryptosporidiosis amongst HIV positive patients presenting with diarrhoea was Cross sectional study also referred to as prevalence study.

3.3 Study population

HIV patients presenting with diarrhoea in Specialist Hospital, Sokoto categorized as

1. HIV positive patients presenting with diarrhoea only
2. HIV and Tuberculosis co infected patients presenting with diarrhoea
3. Both HIV positive and co infected with CD4 below or above 350
4. Both HIV positive and co infected on different drugs combination codes referred to as regimens as follows;
    a. ***1a*** (AZT – 3TC - EFV) for TB/HIV co infected.
    b. ***1b*** (AZT – 3TC - NVP) for HIV infected only.
    c. ***1c*** (TDF –FTC -EFV) for those with Hb < 8g/dl.
    d. ***1d*** (TDF - FTC - NVP) alternate first line due to failure or default.
    e. ***1e***, (TDF – 3TC - EFV) alternate first line due to side effects.
    f. ***1f*** (TDF – 3TC - NVP) for pregnant clients and others

3.3.2 Inclusion criteria

1. HIV screened and confirmed positive patients presenting with diarrhea during follow up visits.
2. Age; all age groups
3. HIV positive patients presenting with diarrhoea whose consent were sought.

3.3.2 Exclusion criteria

HIV positive patient not presenting with diarrhoea or those with diarrhoea whose consent were not sought or did not show willingness to participate in this study

3.4 Sample size determination/source

One hundred and fifty HIV - infected individuals presenting with diarrhoea were recruited among the HIV positive patients who attend the Specialist hospital routinely as well as at interim visits when acutely ill using the formula for calculating sample size below.

$$n = \frac{z^2 \times pq}{d^2}$$

Where

n = Number of samples

z = Standard normal deviation at 95% confidence interval = 1.96

p = Proportion or otherwise previous prevalence of Cryptosporidiosis in a study carried out in, Nigerian to be studied in the study area.

q = Precision limits (0.05)

Therefore

$$n = \frac{(1.96)^2 \times 0.11 \times (1 - 0.11)}{(0.05)^2} = \frac{3.8416 \times 0.11 \times 0.89}{(0.05)^2}$$

$$= \frac{0.422576 \times 0.89}{(0.05)^2} = \frac{0.37609264}{0.0025}$$

$$= 150.437 = 150 \text{ samples}$$

3.5 Sampling technique

Due to the fact that most of the patients visiting the facility have already started their ART, this which has greatly improve their condition and limited the number of HIV patients presenting with diarrhoea. This limitation and has made the choice of sampling technique to avoid bias difficult and as such diarrhoea patients among HIV positive patients were attended and enrolled consecutively as they come for follow up or related intervention when acutely sick.

3.6 Study instrument

Study instruments used for this study were, Hospital general request/ report forms, ART, PMTCT, HCT Laboratory, Clinic and Pharmacy registers. Other instruments were Clinical evaluation and pharmacy order forms

3.6.1 Specimen collection

Faecal Samples were collected in wide mouth plastic containers with UV, Age, sex and consistencies of stool samples were recorded. Samples were examined as were collected.

3.6.2 Materials

These include wide mouth plastic containers with lid, microscope, slides and cover slips, compound microscope, formal saline, centrifuge, centrifuge tubes, seiver, ether, applicator sticks, carbol-fuchsin, hydrochloric acid, methanol, malachite green, cotton wool and immersion oil.

Reagents. Strong Carbol Fuchsin: prepared by dissolving 5g of powdered basic fuchsin in the solution of phenol (containing 25g of phenol with little water) in a boiling water bath, 50ml of alcohol was added and mixed. Malachite Green: prepared by dissolving I gram of powdered malachite green in 1000ml of distilled water.

3.6.3 Parasitological techniques

Direct Wet Preparation

Stool samples were examined by direct techniques as described. The appearance of the specimens were noted, the colour, consistency (formed, semi-formed or watery), the presence of blood, mucus, and worms or their segments. A drop of fresh physiological saline was placed on a glass slide. A piece of stick was used to pick a small amount of the specimen which was mixed with the saline to make a smooth preparation. This was then covered with a cover slip and examined microscopically under x10 and x40 objectives for the presence of parasite cysts, Trophozoites, eggs, or larvae[51].

Formal ether concentration

About 2g of faeces was emulsified in 4mls formal saline solution in centrifuge tube thoroughly. The faecal suspension was then sieved, and 2ml of ether was added and shaken. The mixture was then centrifuged at 1000 rpm for 2 minutes. Using an applicator stick, the debris layer, was loosened and together with supernatant were poured away. The sediment was re-suspended by tapping the bottom of tube smears were then made with sediment[36,51].

Modified Zeil Nelson Staining

The smears made with sediment were stained by the modified Zeil-Nelson staining method.[36,]. The smear was fixed by heat and flooded with carbol fuchsin solution and heated gently until steam rises. This was left for 5 minutes and washed with tap water. It was decolorized with 1% acid alcohol until the film becomes yellowish. It was washed with water and counterstained with malachite green for 3 minutes. It was washed with water, bottled, dried and examined under oil immersion lens for the presence of Oocysts *of Cryptosporidium.*[36,51]

3.7 Data collection method

Trained Laboratory Technician and the researcher collected al the information used in this study using HIV positive diarrhoea presenting patients registers, forms and records in the facility as source of information.

3.8 Data management

Information obtained from patients and derived from relevant record were captured and written into a text book prior to entry into excel soft were

3.8.1 Measurement of variables

The major measurable considered were age, sex, paraites encountered, CD4 status, drug regimens and stool consistency

3.8.2 Statistical analysis

Data were entered into Excel Microsoft office 2007, cleaned and analyzed for prevalence of cryptosporidiosis among sex and different age groups using Epi info software version 3.5.3 (CDC Atlanta). Descriptive analysis was use to determine parasites prevalence/frequencies. Chi square test was also used to determine levels of association between the variables used in this study.

3.9 Ethical considerations

Ethical clearance was obtained from the Ahmadu Bello University ethical and scientific committee. Permission was also sought from the Sokoto state Agency for the Control of AIDS (SOSACA), the State Ministry of Health Sokoto, Heads of specialist hospital Sokoto (SHS) and relevant stake holders supporting the facility where the study was conducted. Confidentiality of all data from the studied patients were treated with utmost confidentiality. The information of the

patients were used only for research purpose and shared only among the study team and relevant stakeholders.

As the study involve all age groups. For those under the age of eighteen, unconscious and mentally sick, their parents, guidance or caregivers were contacted. Participation in the study was voluntary and all patients including defaulters were treated equally. Patients or relatives, who were illiterates, were asked to make a thumb print in place of signature. All laboratory cost were borne by the researcher and patients that fell sick were referred to a Doctor and results were communicated to the clinic or a Medical officer in the facility. All measures were adapted to maintain safety of health workers that were involved in this study.

3.10 Scope and limitation of the study

The study was primarily concerned with *Cryptosporidium* identified during the period of the research, though other parasites encountered were also reported The study did not employ a PCR-based protocol and florescence labeled monoclonical anti-body for *C. parvum* due to high cost of materials and Floatation technique was not used to concentrate cypto oocyst. The study was limited to the microscopic examination for Oocysts of *Cryptosporidium* in smears made from sediment of formal ether concentration after staining by the modified Ziehl-Nelson staining method.[36,51] The study did not attended to other patients outside those visiting the Sokoto State Specialist Hospital.

CHAPTER FOUR

4.0 Results

A total of 150 HIV patients visiting the Specialist Hospital Sokoto (SHS) with diarrhoea were investigated for Cryptosporidiosis. Out of this number, 65 (43 %) were males and the remaining 85 (57 %) were females (Fig. 1). Crypto was commoner among female patients (2.6) when compared to the male (1.4) prevalence. There is no significant statistical difference between the two groups at 95 % Confidence Limit.

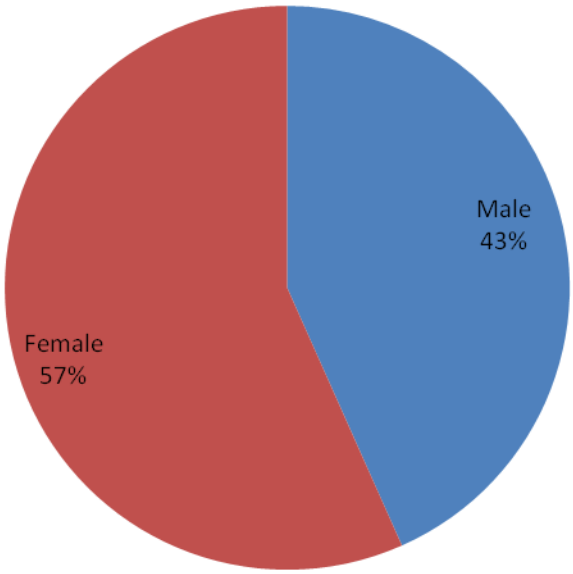


Figure 1; a pie chart showing percentage of patients in relation to sex tested for cryptosporidiosis.

Table 1: Distribution of *Cryptosporidium* by Age and Sex among HIV patients presenting with diarrhoea to the SHS.

	Male(A)			Female(B)			(A+B)
Age groups (yrs)	**No Examined**	**No Positive**	**% Prev.**	**No Examined**	**No Positive**	**% Prev.**	**% Prev**
6-15	3	0	0.0	3	0	0.0	0.0
16-25	11	0	0.0	15	0	0. 0	0.0
26-35	25	0	0.0	30	1	0.6	0.6
36-45	16	1	0.7	23	1	0.6	1.4
46-55	7	1	0.6	12	2	1.4	2.0
56 -60	3	0	0.0	2	0	0.0	0.0
Total	**65**	**2**	**1.4**	**85**	**4**	**2.6**	**4.0**

Mean age 33.7, SD 9.5, Median 30

The age group distribution of *Cryptosporidium* prevalence among HIV infected patients who had diarrhoea was 4.0%. With the highest prevalence among patients aged 46-55years (2.0 %), followed by age group 36 – 45 (1.4 %), then those aged 26 – 35 (0.6 %) when compared to 0.0 % prevalence recorded in those aged 6 -15, 16 – 25 and 56 -60 respectively (Table 1).

Table 2: Distribution of parasites isolated from stool of patients with diarrhea in SHS

Parasite types	Number tested	Frequency	% infected
Cryptosporidium Parvum	150	6	6 (4.0)
Ascaris lumbricides	″	11	11(7.3)
Hook worm	″	5	5 (3.3)
Schistosoma mansoni	″	1	1 (0.7)
Trichuris trichura	″	I	1 (0.7)
Entamoeba histofytica	″	10	10(6.7)
Total	**150**	**34**	**34 (22.7)**

The overall parasite prevalence of Human intestinal parasites encountered in the study rate 22.7% (34/150) with *Cryptosporidium parvum* 4.0%, *Ascaris lumbricoides* 7.3%, *Hookworm* 3.3%, *Schistosoma mansoni* 0.7%, *Trichuris trichura* 0.7% and *Entamoeba histolytica* 6.7% (Table 2).

Table; 3 Prevalence of Cryptosporidiosis among drugs combination regiment

REGIMEN	No Tested	No. positive	Percent positive
1A	108	3	2.0 %
1B	3	0	0.0 %
1C	2	0	0.0 %
1D	2	1	0.7%
1E	3	0	0.0 %
1F	32	2	1.3 %
Total	**150**	**6**	**4.0 %**

Confidence limits: 0.41 – 5.7 %**,** 0.16 – 4.73 %, and 15.07 – 28.76 %

On the other hand, the prevalence of Crypto among different drugs regimen (combination) was found to be higher among Regimen 1A which is usually meant for HIV/TB co – infected

patients. The prevalence of 2.0 % (3) was recorded among HIV patients with diarrhoea on 1A regiment, followed by 1F 1.3 (2), then 1D 1 (0.7) and 0.0 % recorded encountered with HIV diarrhoea patients on regimen 1A, 1C and 1E. there is significant difference between 1A and 1B, 1C and 1E as 1A and 1F did not differ significantly at 95% confidence limit (Table 3).

Table 4; Prevalence of Cryptosporidiosis in relation to HIV patients CD4 group

CD4GRP	No tested	No positive	Percent positive
>0 - 350	139	4	2.7 %
>350 - 700	11	2	1.3%
Total	147	6	4.0%

C. I = 2.38% - 10.44%

The observed prevalence among CD4 groups showed higher prevalence 2.7 % among HIV patients with diarrhoea whose CD4 is below 350 who at the same time formed majority of the patients tested (139 patients) compare to the least prevalence 1.3 % recorded among patients with CD4 greater than 350. There is observed significant statistical difference between the two categories. (Table 4)

Table 5; Prevalence of Crypto in relation to stool Consistency

	Diarrhoea with Blood		**Total**	
	Yes	No	**NO.**	**%**
Cryptosporidium	6 (4.0 %)	0	6	4.0 %
No Cryptosporidium	0 (0.0%)	144	144	96 %
Total	6	144	150	100 %

OR 1.03, 95% CI 0.20 85.27, P - VALUE 0.7 144 (47.3%)

Prevalence of Crypto in relation to stool consistency showed that, all the 4.0 % of crypto encountered among HIV patients with diarrhea and blood only, OR 1.03, 95% CI 0.20 85.27, P - value 0.7 when compared to 0.0 % Crypto prevalence recorded among diarrhea with blood and mucus and diarrhea with mucus only (Table 5).

CHAPTER FIVE

5.0 Discussion

Diarrhoea is a significant problem in HIV-infected patients in Africa.[4,53,54], *Cryptospcridium* is a well established cause of diarrhoea among HIV infected patients worldwide with prevalence of infection ranging from 3% in developed countries to 50% in developing countries.[5,43,55]. However, the role of this parasite in the occurrence of diarrhoea among all age groups of patients with HIV infection in Sokoto State, Nigeria is not established.[56]

Higher prevalence of *Cryptosporidium* was observed in females than males. This may be attributed to higher prevalence of HIV-1 in females than males as reported elsewhere.[53,57]. The relatively high prevalence of HIV/AIDS in women of child-bearing age is of particular concern, given the possibility of vertical transmission from mother to child and the strong association between HIV/AIDS and Cryptosporidiosis. However, in other studies, the prevalence of *Cryptosporidium* was reported to be higher in males than females.[3451,58].

The result of this study showed higher prevalence among those aged 46 -55 (2.0 %) which is statistically significant when compared to the rest of the age groups female sex. It is likely that variation in prevalence among age groups is associated with levels of exposure, practices or behaviors in the community that exhibit temporal variation. In contrast, other studies in the tropics have indicated that prevalence of infection is highest in age group 15 – 26. Although, the mechanism by which *Cryptosporidium* cause diarrhoea is not well known. Inflammatory response to the infection is variable and may be modified by co-pathogens such as *Cryptosporidium.* However, histologic evidences of gastrointestinal mucosa injury has been

reported with clinical manifestations influenced in part by the anatomic distribution of the infection with extensive infections involving both small and large intestinal producing the most severe illness.[1,34,59]

A study carried in a tertiary institution in Southeastern Nigeria.[31,33,37,43] using modified Ziehl Nelsen Staining Technique, *Cryptosporidium* was not detected in stool samples in 189 HIV infected and non-infected patients with diarrhoea. This contrasts this finding using the same detection method were an overall *Cryptosporidium* prevalence of 4.0% is reported and 6.0% prevalence rate among HIV infected patients. The reason for this difference can be related to the known fact that HIV opportunistic infections, Cryptosporidiosis inclusive, tend to vary from one locality to another and from one country to the other depending on the level of contamination of water, food stuff and contacts with animals which are important factors in dissemination of the parasite[8] .Cryptosporidiosis in Nigeria has been reported from tertiary institutions mainly among children in North-central[15] and [53].

This study appears to be the first from Sokoto in North western Nigeria. The *Cryptosporidium* prevalence rate of 4.0% reported among these diarrhoea patients is quite similar to rate reported from a tertiary institution in South East Nigeria[37,] It is also similar to rates reported[46], who found a prevalence of between 1-4% among diarrhoea patients in developing and developed countries.[46]. This prevalence is however low compared to 38% recorded for *Cryptosporidium* infection among HIV infected patients in Haiti[55]. The low prevalence recorded in this study may be due to the small sample size and the fact that some of the patients are receiving anti-retroviral therapy and therefore have improved immune responses.

The highest prevalence (2.0 %) of Cryptosporidiosis encountered among those client on 1A drugs combination regiment (Zidovudine, Lamodovdine and Efavirenz) could be attributed to the fact that those group already are co - infected with Tuberculosis and as such paves way for other opportunistic infections[19,20,21,22], coupled with the fact that, the group constituted majority of the clients visiting the facility with diarrhea as the prevalence was higher among those with CD4 count less than 350 when compared to those group with CD4 4 above 350.[59]

On the other hand, the findings of this study quite disagrees with most of the literature review stating that, Cryptosporidiosis is associated with mucus in the stool as all the crypto encountered in this study were among diarrhea with blood or blood and mucus watery stool. No cryptosporidium cyst was encountered from diarrhea with mucus faeces only.

This study has few limitations, this is because only a single stool specimen was examined per patient. As a result, the prevalence of infection may have been under estimated[54]. Furthermore, only formal ether concentration technique was used which probably might have destroyed the cyst due to centrifugal force as opposed to floatation technique using zinc sulphate preparation. Other limitations were small sample size due to rareness of diarrhoea patients among HIV positive patients as a result of improved immune response as most of the patients were on ART.

CHAPTER SIX

6.0 Conclusion

Cryptosporidium Oocysts have been demonstrated in faeces of HIV infected patients attending Specialist Hospital. It accounts for 4.0% of diarrhoeal cases among this group. The TB/HIV co infected patients had the highest of occurrence of cryptporidium probably as a result poor immunity and, all the crypto encountered were from patients whose CD4 were below 350. Similarly, all the crypto encountered were from diarrhoea with mucus as no crypto was found amongst bloody watery stool samples. This study provides baseline data on the prevalence of Cryptosporidiosis among HIV infected patients presenting with diarrhea and the relationship between CD4 and ART regimen and opportunity for further research on immuno suppressed patients in the study area and Sokoto state at large.

6. 1 Recommendations

Bases on the results obtained from this study, the following recommendations are made.,

1. It is recommended that information/findings obtained from this study be used in establishing base line information and for implementing control/prevention intervention against parasitic opportunistic infections or related infections affecting the vulnerable group (HIV patients) in Sokoto State.
2. All stakeholders working in area of HIV/AIDS in Sokoto State to improve massive mobilization on the importance of standard personal hygiene among HIV positive clients in the study site and the State at large with a view to reduce the risks of contracting parasitic infections among People Living with HIV viruses.

3. Partners and service care providers to focus on utilizing Laboratory services for the accurate diagnosis and detection of all forms of Opportunistic Infections ranging from Bacteria, Fungi, other viral infections and parasitic infections aim at managing diarrheal diseases among HIV and other immuno-suppressed patients
4. More research is recommended to be conducted on parasitic infections among PLWHIV
5. It is also recommended that Govt. and partners to focus on free medication for OIs among PLWHIV similar to ART services such as counseling, testing, palliative care and antiretroviral therapy which all have rendered free to the public at the same time, ensure the sustainability of interventions
6. . It is further recommended that Govt. and partners to improve training programs for health workers and educate them on the proper treatment of diarrhea, ensure that facilities for hand washing, proper disposal of human waste are provided at all healthcare facilities not only those offering comprehensive HIV/AIDS services and Promote hand washing.

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APPENDIXES I

Department Of Community Medicine,

Ahmadu Bello University, Zaria.

Research On Cryptosporidiosis among HIV patients presenting with dearrhoea in Specialist Hospial Sokoto: (A Cross sectional study among patients attending HIV/AIDS comprehensive site in Specialist Hospital Sokoto State, Nigeria

Consent form for the Respondents

I am undertaking a study to determine the prevalence of Cryptosporidiosis, a parasitic infection responsible for most severe diarrhoea among HIV patients resulting among majority of People Living with HIV/AIDS in accessing services at the Sokoto State Specialist Hospital.

You are free to or not to participate in the study, but we will benefit from it if you volunteer to participate in this study greatly as your participation will help in understanding the problem better and provide useful information that will assist in designing targeted public health interventions for the prevention and control of diarrhoea associated with *Cryptosporidium parvum* among People Living with HIV accessing HIV services in Specialist Hospital Sokoto.

If you have decided to enrol, I wish to ask you some questions which will last for about 25 minutes.

Consent obtained? Yes ☐ No ☐

If yes,

Signature or right thumb print of the respondent/date

….....……..

Witness:

Name: ……..

Signature/Date ……

APPENDIXES 11

Sashen Kula da Lafiyar Al'umma

Jami'ar Ahmadu Bello, Zaria

Bincike kan kwayar cutar da ke yawan sa gudanawa mai tsanani tsakanin akasarin wadanda ke dauke da kwayar cutar Sida mai karya garkuwar jiki masu da ke amsar kulawa Asibitin kwararru ta Sokoto.

Zuwa Ga Masu amsa Tambayoyi a cikin wannan bincike,

Ina yin wannan bincike ne don gano adadin wadnda ke kamuwa da gudanawa sanadin kamuwa da kwayar cutar da ake kira "Cryptosporidium" da turanci tsakanin wadanda ke fama da ciyon da ke karya garkuwar jiki a cikin wadanda ke amsar kulawa a asibiti kwararru ta Sokoto.

Kana/kina da dammar ka/ki shiga wannan bincike, tabbas za ka/ki umfana idan ka/ke shiga cikin wannan bincike, saboda bada hadin kan ka/ki zai taimaka wajen fahintar wannan kwayar cutar da ke sa a kasarin masu dauke da kwayar cutar Sida gudanawa tsakanin masu amsar kulawa a asibitin kwararru ta Sokoto.

Idan ka/ke amince, zan yi maka/miki wasu 'yan tambayoyi wanda za su iya kaiwa tsawon mintota ashirin da biyar.

Idan ka/ke aminta ba da tilastawa ba, za ka/ki ba da bayanai ga wannan binciken da muke yi domin neman bayani a gareka/ki.

To, na amince ☐ **Aa, ban amince ba** ☐

Idan ka/ke amince:

Suna……

Ka sa hannu ko ka dangwala babban dan yatsa na dama anan/kwanan wata

……

Shaida:

Suna……

Sa hannu da kwanan wata…….

APPENDIX 111

Adult Initial Clinical Evaluation

Patient Surname _____ **Other names** _____

Unique ID ☐☐☐ ☐☐☐ ☐☐☐☐☐ **Hospital(Unit) No** _____

30. Previous ARV exposure (probe)
- ○ Transfer in with records
- ○ Earlier ARV but not a transfer in
- ○ PMTCT only
- ○ None

31. Current medications (probe and specify)
- ○ None
- ○ ART
- ○ TMX/SMX
- ○ Anti-TB drugs
- ○ Other (specify)

32. Service entry into program:
- ○ STI ○ Private ○ ANC/PMTCT
- ○ OPD ○ TB ○ Current clinic patient
- ○ HCT ○ Ward ○ Self-referral
- ○ HBC ○ Casualty ○ Substance use

33. Adherence

a. Participating in an adherence program ○ Y ○ N
-Missed ARV in the last 3 days: ○ Y ○ N

☐ Enter code for why patient **missed** medication

b. Treatment was **interrupted** ○ Y ○ N
Date ___/___/___ Number of days ☐☐
☐ Enter code for why patient **interrupted** medication

c. Treatment was **stopped** ○ Y ○ N
Date ___/___/___ Number of days ☐☐
☐ Enter code for why patient medication was **stopped**

Reason codes:	9 Toxicity
1 Felt good	10 Drug interaction
2 Forgot/slept through	11 Ran out of medication
3 Couldn't adhere to schedule	12 Drugs not available
4 Patient preference	
5 Stigma of HIV/AIDS	14 Clinical Failure
6 Doctor's instruction	15 Immunologic Failure
7 Never went back	16 Virologic Failure
8 Patient moved	17. Other (Specify) _____

34. Patient has disclosed status to:
- ○ No one ○ Friend
- ○ Family member ○ Spouse
- ○ Spiritual leader ○ Other _____

35. HIV status can be discussed with : _____
_____
(record reported person, if any)

36. Is patient a member of a support group? ○ Y ○ N

37. Past or current ARV side effects ○ None
- ○ Signif. nausea/vomit
- ○ Headache
- ○ Diarrhea
- ○ Pain abdomen or muscle
- ○ Insomnia / bad dreams
- ○ Confusion/dizzy
- ○ Tingling of extremities
- ○ Rash
- ○ Jaundiced
- ○ Steven Johnson syndrome
- ○ Itching
- ○ Anemia
- ○ Weakness/fatigue
- ○ Pancreatitis
- ○ Fat accumulation or loss
- ○ Hyperglycemia
- ○ Kidney problems
- ○ Liver problems
- ○ Other (specify) _____

38. Physical exam *(note: NSF= no significant findings)*

Temp: ___ °C | **BP** ___/___ mm/Hg | **Pulse** ___ | **Wt** ___ kgs | **Ht** ___ m

General appearance ○ NSF
- ○ Pallor
- ○ Febrile
- ○ Dehydrated
- ○ Jaundiced
- ○ Peripheral edema
- ○ Other (specify)_____

Skin ○ NSF
- ○ Pruritic paplar dermatitis
- ○ Abscesses
- ○ Herpes zoster
- ○ Kaposi's lesions
- ○ Suborrheic dermatitis
- ○ Fungal infections
- ○ Other (specify) _____

Head/Eye/ENT ○ NSF
- ○ Icterus
- ○ Thrush
- ○ Oral KS _____
- ○ Abnormal fundoscopy
- ○ Other (specify)_____

Breasts ○ NSF
- ○ Lumps, masses
- ○ Discharge
- ○ Other (specify)_____

Cardiovascular ○ NSF
- ○ Abnormal heart rate
- ○ Auscultation finding
- ○ Other (specify) _____

Genitalia ○ NSF
- ○ Genital discharge
- ○ Genital ulcer/other lesion
- ○ Inguinal node enlargement
- ○ Other (specify) _____

Respiratory ○ NSF
rate _____ breaths/min
- ○ Labored breathing
- ○ Cyanosis
- ○ Wheezing
- ○ Intercostal (sub) recession
- ○ Auscultation findings
- ○ Other (specify)_____

Gastrointestinal ○ NSF
- ○ Distention
- ○ Hepatomegaly
- ○ Spenomegaly
- ○ Tenderness
- ○ Other (specify) _____

Neurological ○ NSF
- ○ Orientation to TPP
- ○ Speech slurs
- ○ Neck stiffness
- ○ Blindness 1/2 eyes
- ○ Hemiplegia/paresis
- ○ Numbness of extremities
- ○ Other (specify)_____

Mental status ○ NSF
- ○ Slow mentation
- ○ Memory loss
- ○ Mood swings
- ○ Depression
- ○ Anxiety
- ○ Suicidal ideation
- ○ Other (specify)_____

Additional and detailed findings:

39. Assessment ○ Asymptomatic ○ Symptomatic ○ AIDS defining illness/opportunistic infection

APPENDIX III CONT'D

Patient Surname _____ Other names _____

Unique ID [ ][ ][ ] [ ][ ][ ] [ ][ ][ ][ ][ ] Hospital(Unit) No _____

State Facility No Serial enrollment No

40. WHO staging criteria (History of any of the following)

Stage 1
- ○ Asymptomatic
- ○ Persistent generalized lymphadenopathy
- ○ Performance scale: 1 asymptomatic, normal activity

Stage 2
- ○ Weight loss <10% of body weight
- ○ Minor Mucocutaneous Manifestations
- ○ Herpes Zoster (within last 5 years)
- ○ Recurrent Upper Respiratory Tract Infections
- ○ Performance scale: 2 symptomatic, normal activity

Stage 3
- ○ Weight loss >10% of body weight
- ○ Unexplained Chronic Diarrhea (>1 month)
- ○ Unexplained Prolonged Fever
- ○ Oral Candidiasis
- ○ Oral Hairy Leukoplakia
- ○ TB, Pulmonary (within previous year)
- ○ Severe Bacterial Infections
- ○ Performance scale: 3 bedridden <50% of day in last month

Stage 4
- ○ HIV Wasting syndrome
- ○ PCP
- ○ Toxoplasmosis, CNS
- ○ Cryptosporidiosis with Diarrhea (>1 month)
- ○ Cryptococcosis, Extrapulmonary
- ○ Cytomegalovirus disease
- ○ Herpes Simplex (mucotaneous >1 month)
- ○ Progressive Multifocal Leukoencephalopathy
- ○ Mycosis, disseminated
- ○ Candidiasis
- ○ Atypical Mycobacteriosis, disseminated
- ○ Salmonella Septicemia, Non-typhoid
- ○ TB, Extrapulmonary
- ○ Lymphoma
- ○ Kaposi's Sarcoma
- ○ HIV encephalopathy
- ○ Performance scale: 4 bedridden >50% of the day in last month

41. WHO Stage [ ]

42. Plan (specify orders on requisition)

- ○ Lab evaluation _____
- ○ Screen for tuberculosis _____
- ○ OI Prophylaxis _____
- ○ Post Exposure Prophylaxis (PEP) _____
- ○ Adherence counseling _____
- ○ CI therapy _____
- ○ Admission _____
- ○ Symptomatic treatment/pain control (specify) _____
- ○ Other referrals (specify) _____

43. Enroll in: ○ General medical follow-up ○ ARV therapy ○ Pending lab results

44. ARV therapy

- ○ Continue current treatment
- ○ Restart treatment
- ○ Start new treatment
- ○ Ongoing monitoring –ARV Tx not indicated
- ○ Ongoing monitoring –ARV Tx post-poned for clinical reasons
- ○ Change treatment (indicate reason code) [ ]
- ○ Stop treatment (indicate reason code) [ ]

45. a. Regimen

1st Line	Alternate	2nd Line	Others
○ d4T/3TC/NVP	○ TDF/3TC/EFV	○ _____	○ _____
○ d4T/3TC/EFV	○ TDF/3TC/NVP	○ _____	○ _____
○ ZDV/3TC/EFV		○ _____	○ _____
○ ZDV/3TC/NVP		○ _____	○ _____

45 b. Drugs in regimen _____ / _____ / _____

46 a. Patient has received care for HIV/AIDS from:

- ○ None received ○ Self-pay
- ○ Gov't sponsored pgm ○ USG sponsored program
- ○ Mission/faith based ○ This facility

46 b. Specify facility name _____

47. Next appointment?

- ○ 1 week ○ 2 months
- ○ 2 weeks ○ 3 months
- ○ 4 weeks

_____ / _____ / 20_____ dd/mm/yyyy

Clinician's name (Print) _____ **Signature** _____

Appendix iii continued.

Patient Surname _____ Other names _____

Unique ID ☐☐☐ ☐☐☐ ☐☐☐☐☐ Hospital(Unit) No _____
State Facility No Serial enrollment No

40. WHO staging criteria (History of any of the following)

Stage 1
- ○ Asymptomatic
- ○ Persistent generalized lymphadenopathy
- ○ Performance scale: 1 asymptomatic, normal activity

Stage 2
- ○ Weight loss <10% of body weight
- ○ Minor Mucocutaneous Manifestations
- ○ Herpes Zoster (within last 5 years)
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- ○ Performance scale: 2 symptomatic, normal activity

Stage 3
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- ○ Oral Candidiasis
- ○ Oral Hairy Leukoplakia
- ○ TB, Pulmonary (within previous year)
- ○ Severe Bacterial Infections
- ○ Performance scale: 3 bedridden <50% of day in last month

Stage 4
- ○ HIV Wasting syndrome
- ○ PCP
- ○ Toxoplasmosis, CNS
- ○ Cryptosporidiosis with Diarrhea (>1 month)
- ○ Cryptococcosis, Extrapulmonary
- ○ Cytomegalovirus disease
- ○ Herpes Simplex (mucotaneous >1 month)
- ○ Progressive Multifocal Leukoencephalopathy
- ○ Mycosis, disseminated
- ○ Candidiasis
- ○ Atypical Mycobacteriosis, disseminated
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- ○ TB, Extrapulmonary
- ○ Lymphoma
- ○ Kaposi's Sarcoma
- ○ HIV encephalopathy
- ○ Performance scale: 4 bedridden >50% of the day in last month

41. WHO Stage ☐

42. Plan (specify orders on requisition)
- ○ Lab evaluation _____
- ○ Screen for tuberculosis _____
- ○ OI Prophylaxis _____
- ○ Post Exposure Prophylaxis (PEP) _____
- ○ Adherence counseling _____
- ○ CI therapy _____
- ○ Admission _____
- ○ Symptomatic treatment/pain control (specify) _____
- ○ Other referrals (specify) _____

43. Enroll in: ○ General medical follow-up ○ ARV therapy ○ Pending lab results

44. ARV therapy
- ○ Continue current treatment ○ Restart treatment ○ Start new treatment
- ○ Ongoing monitoring –ARV Tx not indicated ○ Ongoing monitoring –ARV Tx post-poned for clinical reasons
- ○ Change treatment (indicate reason code) ☐ ○ Stop treatment (indicate reason code) ☐

45. a. Regimen

1st Line	Alternate	2nd Line	Others
○ d4T/3TC/NVP	○ TDF/3TC/EFV	○ _____	○ _____
○ d4T/3TC/EFV	○ TDF/3TC/NVP	○ _____	○ _____
○ ZDV/3TC/EFV		○ _____	○ _____
○ ZDV/3TC/NVP		○ _____	○ _____

45 b. Drugs in regimen _____ / _____ / _____

46 a. Patient has received care for HIV/AIDS from:
- ○ None received ○ Self-pay
- ○ Gov't sponsored pgm ○ USG sponsored program
- ○ Mission/faith based ○ This facility

46 b. Specify facility name _____

47. Next appointment? ○ 1 week ○ 2 months ○ 2 weeks ○ 3 months ○ 4 weeks _____ / _____ / 20_____ dd/mm/yyyy

Clinician's name (Print) _____ **Signature** _____

Appendix iv

Adult Pharmacy Order Form

○ ART ○ Non-ART ○ Occup PEP ○ Non-Occup PEP ○ PMTCT ○ Initial Visit ○ Follow-Up Visit

Visit date (dd/mm/yyyy) ____ / ____ /20__ (dd/mm/yyyy)

Patient Name [ ] (Surname) [ ] (Other Name(s)) Age [ ] years Sex: Male ☐ Female ☐

State ________ LGA ________ Facility Name ________

Unique ID ☐☐☐☐☐☐☐☐☐☐☐☐☐☐ Hospital (Unit) No. [ ]

Pharmacy Registration No. ________ Weight ______ Kg Height ______ m

○ DO NOT DISPENSE ARV'S TO PATIENT; HOLD FOR ADHERENCE STAFF PICKUP

○ Pregnant ○ Refill Fastrack ______ ○ Substitution ○ Switch

1. ARV Medications	Strength	Frequency	Duration	Qty Prescribed	Qty Dispensed
Zidovudine (AZT, ZDV; Retrovir)	○ 100 mg ○ 300 mg	○ 3 BD ○ BD			
Lamivudine (3TC; Epivir)	○ 150 mg ○ 300 mg	○ BD ○ OD			
Abacavir (ABC; Ziagen)	○ 300 mg	○ BD			
Emtricitabine (FTC; Emtriva)	○ 200 mg	○ OD			
Tenofovir (TDF; Viread)	○ 300 mg	○ OD			
Combivir (AZT + 3TC)	○ 300mg/150mg	○ BD			
Truvada (TDF + FTC)	○ 300mg/200mg	○ OD			
Tenofovir+Lamivudine (TDF+3TC)	○ 300mg/300mg	○ OD			
Nevirapine (NVP; Viramune)	○ 200 mg (for 1st 2 wks, then BD dosing) ○ 200 mg	○ OD ○ BD			
Efavirenz (EFV; Sustiva, Stocrin)	○ 600 mg ○ 200 mg ○ 800 mg	○ Nocte ○ 3 Nocte ○ OD (if on rifampicin)			
Nelfinavir (NFV; Viracept)	○ 250 mg ○ 5 BD	○ ______			
Indinavir (IDV; Crixivan)	○ 400 mg ○ 200 mg	○ 2 BD (w/ RTV) ○ 4 BD (w/ RTV)			
Ritonavir (RTV; Norvir)	○ 100 mg	○ BD			
Saquinavir (SQV; Fortovase, Invirase)	○ 200 mg	○ 5 BD (w/ RTV)			
Alluvia (LPV/r; lopinavir + ritonavir)		○ 2 BD ○ 4 BD (w/ NNRTI)			
Atazanavir boosted(ATV/r)	○ 300 mg	○ OD			
2. Drugs for OI Prophylaxis					
CTX	○ 480 mg ○ 960 mg	○ OD ○ 3x/wk			
Fluconazole	○ 200 mg	○ 2 BD ○ BD			
Dapsone	○ 100 mg	○ OD			
INH/B6	○ 300 mg/50 mg	○ OD			
3. Anti-TB Drugs					
INH	○ 300 mg ______	○ OD			
Rifampicin	○ 300 mg ______	○ OD			
Ethambutol	○ 400 mg ______	○ OD			
PZI	○ 400 mg ______ ○ 600 mg ______	○ OD ○ OD			
Streptomycin injection	○ 1g ______	○ OD			
4. Other drugs not listed above					
______					
______					
______					
______					
______					

________ Ordered by (Print Physician's Name) ________ / /20 Signature & Date ________ Dispensed by (Print Pharmacist's Name) ________ / /20 Signature & Date

________ Counseled by (Print Adh. Counselor's Name) ________ / /20 Signature & Date ________ Picked up by (Print Name) ________ / /20 Signature & Date

Feedback from the Pharmacist in case of any observed prescription error (attach additional sheets if needed):

i. Name of the drug(s) ________

ii. Nature of the error(s) ________

iii. Consequence(s) of the error ________

iv. Signature and date ________

Harmonized Pharmacy Order Form- June 2011

Appendix v

GENERAL REQUEST/REPORT FORM

(USE FOR STOOL ANALYSIS)

SPECIALIST HOSPITAL SOKOTO

General Request/Report Form

Surname	First Name	Age	Sex	Ward/Clinic	Hospital No.

Clinical Diagnosis	Investigation Required	Specimen	M.O. I/C Date

REPORT

Lab No	Date Received	Date Despatched	Technologist

Appendix vi

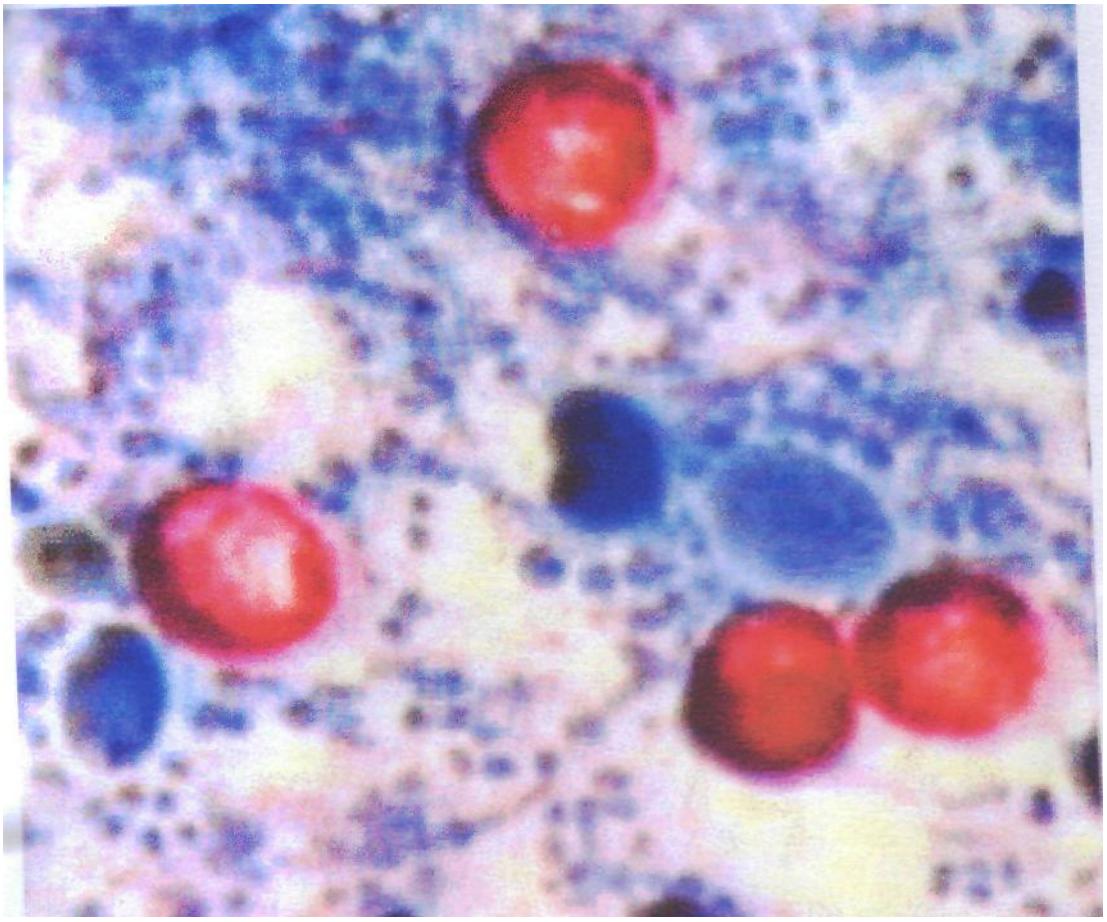


Fig 3**:** Showing Oocysts of *Cryptosporidium* in a positive slide.

Appendix vii

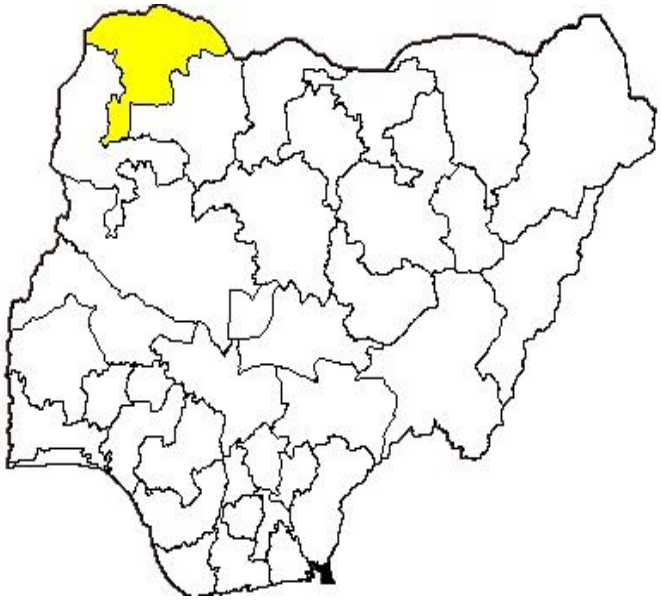


Fig 3: Map of Nigeria showing the location of Sokoto State

Appendix viii

SOKOTO STATE AGENCY FOR THE CONTROL OF AIDS AND TBL

OFFICE OF THE EXECUTIVE GOVERNOR

BLOCK 14 SHEHU KANGIWA SECRETARIAT AHMAD MUHAMMAD DAKU ROAD
P.M.B. 2113 SOKOTO TEL : 234 06-235453
sokotosaca@yahoo.com

The image part with relationship ID rId2 was not found in the file.

Your Ref:.....
Date:.....

Dear Abubakar Aliyu Danmafara,
Dept of Community Medicine,
Ahmadu Bello University, Zaria.

16/7/2012

AKNOWLEDGEMENT/ APPROVAL LETTER

Reference to your letter requesting for approval to conduct a research work on ***"CRYPTOSPORIDIOSIS AMONG HIV PATIENTS PRESENTING WITH DIARRHOEA ATTENDING SPECIALIST HOSPITAL SOKOTO"*** dated 2nd July 2012, the Sokoto State Agency for the Control of AIDS, Tuberculosis and Leprosy (SOSACA) have met with all relevant stakeholders working in the comprehensive site of the Specialist Hospital Sokoto on 5th of July 2012 and resolved to give you the go ahead to conduct the research. However, we agreed that at no point should any member of the support groups be charged for any services in relation to your research as services for all categories of HIV patients are free. Furthermore we would be glad if clients/volunteers are not stigmatized as stigma still remains one of the issues our response is addressing.

With this development, you are therefore given approval to conduct the research and hoping you will share your findings with all relevant stake holders please.

16/7/2012

Sadiq Abubakar Dandin – Mahe,
Community Mobilization Officer,
For: Executive Secretary, SOSACA.

Ethical approval by the Sokoto State Agency for the Control of AIDS

Appendix ix

Ethical approval by the Ahmadu Bello University Teaching Hospital Zaria. research

Ahmadu Bello University Teaching Hospital
P.M.B. 06, Shika - Zaria, Kaduna State, Nigeria. 069-876305
website: www.abuth.org abuthshika@yahoo.com Abuthshika@gmail.com

Chairman of Board:
Chief Medical Director: DR. LAWAL KHALID, *MBBS, FMCS, FWACS, FRCS(ED) mni*
Chairman, Medical Advisory Committee: DR. ABDULLAHI MOHAMMED, *MBBS, FWACP FICS*
Director of Administration: BARR. ISHAK BELLO, *LL.B, BL, LL.M, PGDM, AHAN, FCAI*

Our Ref:

ABUTH/HREC/TRG /36

15TH May, 2013

FULL ETHICAL CLEARANCE AFTER COMMITTEE REVIEW

Re: ***"Prevalence of Cryptosporidiosis among HIV patients presenting with diarrhoea in specialist Hospital Sokoto proposed study"***

ABUTH Ethics Committee assigned number:	-	ABUTH/HREC/E24/2013
Name of the principal Investigator:	-	Abubakar, Aliyu Danmafara
Address of the Principal Investigator:	-	Dept. Comm. Medicine, A.B.U Zaria.
Date of meeting when final determination on ethical approval was made:	-	13th – 14th February, 2013.

This is to inform you that the research described in the submitted protocol, the consent forms, and other participant information materials have been reviewed and ***given full approval by the ABUTH Ethics Committee.***

Please note: this approval dates from ***15th May, 2013*** to ***15th May, 2014***.

No participant recruitment into this research may be conducted outside these dates.

All informed consent forms in this study must carry the ABUTH HREC number assigned to this research and the duration of ABUTH HREC approval of the study.

This HREC expects that you submit your application as well as an annual report for ethical clearance renewal 3 months prior to expiration of study dates. This is to enable you obtain renewal of your approval and avoid interruption of your research.

If there is delay in starting the research, please inform the ABUTH HREC so that starting dates can be adjusted accordingly.

No changes are permitted in the research without prior approval by ABUTH HREC, except in circumstances outlined in national code for Health Research Ethics:http://www.nhrec.net.

ABUTH HREC reserves the right to conduct compliance assessment visits to your research site without prior notification.

Prof. J.U. Okpapi 15/05/13
Chairman, ABUTH HREC