DECLARATION

This dissertation is my original work and has not been presented for a degree awarded in any University.

Dr. Francis. M. Malwal, B.Pharm

U59/76381/2009

Signature..... **Date**..20/11/2011

SUPERVISORS

This dissertation has been submitted for examination with our approval as university supervisors

1. **Prof. Gichuru Muriuki, PhD**

   Department of Pharmacology & Pharmacognosy

   School of Pharmacy, University of Nairobi (Kenya)

   Signed..... Date..22.11.11.....

2. **Dr. Shital Maru , M.Pharm**

   Department of Pharmaceutics & Pharmacy Practice

   School of Pharmacy, University of Nairobi (Kenya)

   Signed ..... Date..20/11/2011.....

3. **Dr. E.M Mwangangi , M.Pharm**

   Department of Pharmaceutics & Pharmacy Practice

   School of Pharmacy, University of Nairobi (Kenya)

   Signed..... Date..22/11/2011.....

DEDICATION

To the spirit of **Late Dr.John Garang** for his effort during the struggle period and setting the foundation of the Republic of South Sudan, may his soul rest in peace.

To my family for the time that they have sacrificed, so this dissertation would become a reality.

To my wife, Madam Aluk Victor and lovely son Mathiang for their continued sacrifice and understanding

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LIST OF ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
ART	Antiretroviral Therapy
AZT	Zidovudine
CCC	Comprehensive Care Center
CDC	Central for Disease Control and Prevention
CMV	Cytomegalovirus
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
D4T	Stavudine
DDI	Didanosine
EFV	Effavirenz
HAART	Highly Active Antiretroviral Therapy
KNH	Kenyatta National Hospital
LPV/r	Lopinavir /ritonavir
MAC	Mycobacterium avium complex
MMWR	Morbidity and Mortality Weekly Report
NHL	Non Hodgkin Lymphoma
NVP	Nevirapine
OIs	Opportunistic Infections
PCP	Pneumocystis pneumonia
PLHA	People Living with Human Immunodeficiency Virus

RNA	Ribonucleic Acid
SPSS	Statistical Package for Social Sciences
TDF	Tenofovir
TMP-SMX	Trimethoprim Sulfamethoxazole
UNAIDS	United Nations programme on HIV/AIDS

ABSTRACT

Background: Advanced HIV infection may be complicated by opportunistic infections (OIs) and other consequences of immune dysfunction. Often, OIs constitute the first manifestation of HIV infection, indicating significant immunodeficiency. Most of HIV/AIDS morbidity and mortality are attributed to OIs associated with low immune status.

Objective: The main objective of this study was to establish the prevalence of HIV-related OIs in adult patients at Kenyatta National Hospital Comprehensive Care Centre (KNH-CCC).

Study design: This was a hospital-based cross-sectional study conducted between July and August 2011 at KNH-CCC. Three hundred and eleven patients' files meeting the inclusion criteria were checked for OIs recorded by the attending clinician on the index visit. Data was analyzed using SPSS version 11.5.

Results: The prevalence of opportunistic infections was 14.1 % (95% CI: 10.7-18.5). Overall, the most commonly reported bacterial infection was pneumonia (6.4%) whereas pulmonary tuberculosis was reported in 3.9% of patients. On multivariate analysis significant association was found between a patients' current OI status and WHO stage when HIV was diagnosed (AOR= 3.79 [95% CI = 1.43 – 10.03], P=0.007) and duration since HIV diagnosis (AOR 3.89 [95% CI= 1.58-9.59], P=0.003). Out of the 44 patients with at least one OI, 29.5% of them were not managed according to the Kenya National Manual for the Management of OIs and related Conditions. Co-trimoxazole was the most commonly prescribed chemoprophylaxis agent, used by 90.0% of the patients.

Conclusion: There was a high prevalence of OIs among the HIV/AIDS patients at KNH-CCC. Bacterial Pneumonia and pulmonary tuberculosis were the most commonly observed OIs.

Recommendations: These findings support the recent WHO recommendations to start ART earlier before profound immune destruction occurs. Adherence of health care providers to Kenya National Guideline in management of OIs should be reinforced.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background and epidemiology

There were an estimated 33.3 million people living with Human Immunodeficiency virus (HIV) in 2009, compared with 26.2 million in 1999 [1]. Although the incidence of HIV has been steadily declining since the late 1990s, this decrease is offset by the reduction in AIDS-related deaths due to the significant scale up of antiretroviral therapy (ART) over the past few years. Consequently, the total number of people living with HIV/ AIDS (PLHA) continues to rise.

Sub-Saharan Africa (SSA) still bears an extraordinary share of the global HIV burden with number reaching 22.5 million (68% of the global total) in 2009 [1]. In SSA, there were estimated 1.3 million people who died of HIV related opportunistic infections (OIs) in 2009. This comprised 72% of the global total of 1.8 million deaths attributable to the epidemic [1].

The epidemics in East Africa have declined since 2000 but are stabilizing in many countries [2]. The HIV incidence slowed in Tanzania to about 3.4 per 1000 person-years between 2004 and 2008 [2]. The national HIV prevalence in Kenya also fell from about 14% in the mid-1990s to around 5% in 2006 [3] while AIDS-related deaths fell by 29% between 2002 and 2007 [3].

The scaling up of treatment is profoundly affecting SSA. At the end of 2009, 37% of adults and children eligible for ART were receiving it in the region compared with only 2% seven years earlier [4]. However, most people receiving ART in SSA started treatment late [5]; this limits the overall impact of HIV treatment programmes. Furthermore, the infrastructure, systems and staff required to properly monitor treatment retention and loss are becoming increasingly inadequate as programmes are scaled up.

1.2. Objectives

1.2.1 Goal

To improve the management of HIV/AIDS associated opportunistic infections in HIV–infected adults at Kenyatta National Hospital-Comprehensive Care Center (KNH-CCC).

1.2.2 Broad Objective

To determine the prevalence of opportunistic infections in HIV- infected adult patients at KNH, CCC and to evaluate their management.

1.2.3 Specific Objectives

1. To determine the prevalence of targeted primary opportunistic infections in HIV-infected adults at KNH-CCC.
2. To find out the factors associated with opportunistic infections at KNH-CCC.
3. To find out the management of the targeted Opportunistic Infections at KNH, CCC
4. To compare the OI management at KNH-CCC with the Kenya national guidelines

1.3 Study questions

1. Which are the commonest opportunistic infections (OIs) at KNH, CCC ?
2. Which HAART regimens are associated with more incidences of opportunistic infections?

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1. Human Immunodeficiency Virus (HIV)

HIV is a retrovirus that infects cells of the immune system, destroying or impairing their function. As the infection progresses, the immune system becomes weaker, and the person becomes more susceptible to infections [6].

2.2 .Acquired Immunodeficiency Syndrome (AIDS)

AIDS is defined as the most advanced stage of human Immunodeficiency virus infection. It can take 10-15 years for an HIV-infected person to develop AIDS; antiretroviral drugs can slow down the process even further [6].

2.3. Opportunistic infections (OIs)

Before the introduction and use of Highly Active Antiretroviral Therapy (HAART), opportunistic infections (OIs), which have been defined as infections that are more frequent or more severe because of immunosuppression in HIV-infected persons, were the principal cause of morbidity and mortality in PLHA. In the early 1990s, the use of chemoprophylaxis, immunization, and better strategies for managing acute OIs contributed to improve quality of life and survival [7]. However, the widespread use of HAART starting in the mid-1990s has had the most profound influence on reducing OI-related mortality in HIV-infected persons [7-14].

Despite the availability of HAART in the developed and developing countries, OIs continue to cause considerable morbidity and mortality for three main reasons:

1. Many patients are unaware of their HIV infection and seek medical care when an OI becomes the initial indicator of their disease;
2. Certain patients are aware of their HIV infection, but do not take HAART because of psychosocial or economic factors
3. Certain patients are prescribed Antiretroviral Therapy (ART) , but fail to attain adequate virologic and immunologic response because of factors related to adherence, pharmacokinetics, or unexplained biologic factors [10, 15, 16].

Thus, although hospitalizations and deaths have decreased since the implementation of ART, OIs remain a leading cause of morbidity and mortality in HIV-infected persons [17-25].

HIV leads to immunosuppression that allows opportunistic pathogens to cause disease in HIV-infected persons. OIs and other co-infections that might be common in HIV-infected persons, such as sexually transmitted infections, can also have adverse effects on the natural history of HIV infection. Certain OIs are associated with reversible increases in circulating viral load [26-31], and these increases could lead to accelerated HIV progression or increased transmission of HIV [32].

Thus, although chemoprophylaxis and vaccination directly prevent pathogen-specific morbidity and mortality, they might also contribute to reduced rate of progression of HIV disease. For instance, randomized trials using trimethoprim-sulfamethoxazole (TMP-SMX) have documented that chemoprophylaxis can both decrease OI-related morbidity and improve survival. The survival benefit is likely to be partially attributable to reduced progression of HIV infection [33-

37]. Reduced progression of HIV infection would also indirectly delay or reduce the occurrence of subsequent OIs.

In a cohort of HIV infected patients that was carried at American University of Beirut Medical Center between 1984 and 2008 showed that the incidence of AIDS defining illness among HIV infected patients was 72% (64/89) and most commonly diagnosed OIs were cerebral toxoplasmosis (21%), followed by fungal infections (17%). The majority of AIDs defining illness among HIV infected patients occurred when the CD4 count was less than 200 cells/mm^3[38]. However, the study did not indicate whether the incidence of cerebral toxoplasmosis occurred during prophylaxis or not.

OIs range from relatively minor events (eg oral candidiasis or oral hairy leukoplakia) to sight-threatening episodes of cytomegalovirus (CMV) retinitis, or life-threatening *Pneumocystis jiroveci pneumonia* (PCP). The risk for specific OIs varies with the degree of immunosuppression [39,40,41].Asymptomatic patients with moderate immunosuppression ($CD4^+$ counts 200–500) may become infected with herpes viruses and Candida species and/or develop pneumonias, enteric infections, and meningitis with common pathogens. Massive destruction of the immune system occurs when the $CD4^+$ count is below 200, which increases the risk for opportunistic pathogens (e.g., PCP), opportunistic tumors, wasting, and neurologic complications. With a $CD4^+$ count of 50 to 100, invasive candidiasis, cerebral toxoplasmosis, cryptococcosis, and various protozoal infections are observed. When the $CD4^+$ count falls below 50, the patient is in an advanced immunosuppressed state, which is associated with non-Hodgkin lymphoma (NHL), CMV, and disseminated Mycobacterium avium complex (MAC). Without

treatment, the median survival associated with a $CD4^+$ count below 200 is 3.1 years, and the time to an AIDS-defining infection ranges from 18 to 24 months [39, 41, 42, 43].

With the implementation of HAART, the 3-year probability of AIDS (which includes in many cases OIs) has dramatically declined as compared with before HAART; however, much of this may be attributed to the use of prophylactic regimens for OIs [44].

2.4 Major opportunistic infections in adults

The acquired immunodeficiency syndrome (AIDS) is characterized by the gradual erosion of immune competence and the development of opportunistic infections (OIs) and malignancies. Since the era of HAART began in 1996, AIDS–related mortality has declined in the United States [45, 46]. This decline in mortality more specifically is described by a decline in OIs associated deaths over the pre-HAART (1992–1995), peri-HAART (1996–1999), and post-HAART (2000–2003) eras with an increase in noninfectious AIDS-related mortality[47].

In 1997, the year after HAART initiation, the U.S. Centers for Disease Control and Prevention (CDC) estimated that approximately 60,000 AIDS-related opportunistic illnesses had occurred in the United States during 1996 [45]. This report represents the first calendar year in which the overall incidence of AIDS-associated OIs did not increase in the United States; the 1996 figure represented a decline of 6% compared with 1995.

Patients with HIV infection are susceptible to an array of diseases, but most OIs are caused by a few common pathogens, including *Pneumocystis jiroveci*, *Cytomegalovirus* (CMV), fungi, and *Mycobacteria*. Persons with AIDS also are susceptible to neoplastic diseases (lymphoma and Kaposi sarcoma [KS]) and other conditions, such as wasting syndrome [46, 48].

2.4.1 Pneumocystis pneumonia (PCP)

PCP is caused by *Pneumocystis jiroveci*. Cases cluster among immunosuppressed patients suggesting that pneumocystis spreads through the airborne routes. Disease probably occurs by new acquisition of infection and by reactivation of latent infection [49, 50, 51]. Before the widespread use of primary PCP prophylaxis and ART, PCP occurred in 70%-80% of patients with AIDS [52]; the course of treated PCP was associated with a mortality of 20%–40% in persons with profound immunosuppression. Approximately 90% of cases occurred among patients with CD4+ counts of <200 cells/μL. Other factors associated with a higher risk for PCP included CD4+ cell percentage <14%, previous episodes of PCP, oral thrush, recurrent bacterial pneumonia, unintentional weight loss, and higher plasma HIV RNA [53, 54].

Incidence of PCP has declined substantially with widespread use of prophylaxis and ART; recent incidence among patients with AIDS in Western Europe and the United States is 2–3 cases per 100 person-years [55]. The majority of cases occur among patients who are unaware of their HIV infection or are not receiving ongoing HIV care [56] or among those with advanced immunosuppression (CD4+ counts <100 cells/μL) [57].

2.4.2 Toxoplasma gondii encephalitis

Toxoplasmic encephalitis (TE) is caused by the protozoan *Toxoplasma gondii*. Disease appears to occur almost exclusively because of reactivation of latent tissue cysts [58- 61]. Primary infection occasionally is associated with acute cerebral or disseminated disease.

Seroprevalence varies substantially among different communities (e.g., approximately 15% in the United States and 50%–75% in certain European countries) [61, 62]. In the pre-ART era, for

patients with advanced immunosuppression who were seropositive for *T. gondii* and not receiving prophylaxis with drugs active against *T. gondii*, the 12-months incidence of TE was approximately 33%. The incidence of toxoplasmosis in patients who are seronegative for *T. gondii* is low. If well-documented cases did occur among seronegative patients, they would presumably represent either primary infection, reactivation of latent disease in patients unable to produce detectable antibody, or patients who were tested with insensitive assays. The incidence and associated mortality in Europe and the United States have decreased substantially with the initiation of ART and the broad use of prophylaxis regimens active against *T. gondii* [63, 64].

Clinical disease is rare among patients with CD4+ counts >200 cells/μL. The greatest risk occurs among patients with a CD4+ count <50 cells/μL [58-60, 64]. Primary infection occurs after eating undercooked meat containing tissue cysts or ingesting oocysts that have been shed in cat feces and have sporulated in the environment (sporulation requires at least 24 hours). No transmission of the organism occurs by person-to-person contact.

2.4.3 Cryptococcosis

In the pre-HAART era, cryptococcosis developed in approximately 6% to 10% of AIDS patients in the United States, with meningitis being the most common clinical presentation [65]. In the era of HAART and azole prophylaxis, a significant decline in the incidence of cryptococcosis has been observed [65, 66]. After HIV encephalopathy and toxoplasmosis, cryptococcosis is the most common Central Nervous System (CNS) infection associated with AIDS [65].The initial portal of entry is the lungs, where the organism is normally contained by an intact immune system. Cryptococcal disease typically develops in patients with profound defects in cell-

mediated immunity (i.e., $CD4^+$ counts <100 cells/mm^3). Unlike bacterial meningitis, cryptococcal CNS infection has a much more insidious onset; the most common symptoms are fever and headache. Less frequent signs and symptoms include nausea and vomiting, meningismus, photophobia, and altered mental status. Focal neurologic deficits and seizures are observed in <10% of patients. Cerebrospinal Fluid (CSF) glucose is decreased, whereas CSF proteins are usually elevated. CSF cryptococcal antigen titer and CSF culture are frequently positive.

2.4.4 Mycobacterium tuberculosis

The World Health Organization (WHO) estimates that one-third of the world's population is infected with *Mycobacterium tuberculosis*, resulting in an estimated 8 million new cases of tuberculosis and nearly 2 million deaths each year [67].Approximately 10 million people are estimated to be co-infected with *M tuberculosis* and HIV, and over 90% of these dually infected individuals reside in developing nations. In some areas of sub-Saharan Africa, the rates of co infection exceed 1,000 per 100,000 populations [68]. Worldwide, tuberculosis is the most common cause of death among patients with AIDS, killing 1 of every 3 patients [69].

TB infection occurs when a susceptible person inhales droplet nuclei containing *Mycobacterium tuberculosis* organisms, generated when persons with pulmonary or laryngeal TB disease cough, sneeze, shout, or sing [70]. Usually within 2–12 weeks after infection, the immune response limits multiplication of tubercle bacilli. However, viable bacilli persist for years, a condition referred to as latent TB infection (LTBI). Persons with LTBI are asymptomatic and are not infectious. TB disease can develop immediately after exposure (primary disease) or after

reactivation of LTBI (reactivation disease). Primary disease accounts for one third or more of cases of TB disease in HIV-infected populations [71].

2.4.5 Disseminated Mycobacterium avium complex disease

Organisms of the *Mycobacterium avium complex* (MAC) are ubiquitous in the environment [72, 73, 74]. M. avium is the etiologic agent in >95% of patients with AIDS who acquire disseminated MAC disease [72, 75 - 80]. An estimated 7%–12% of adults have been previously infected with MAC, although rates of disease vary in different geographic locations [72, 76, 79, 80]. Although epidemiologic associations have been identified, no environmental exposure or behavior has been consistently linked to a subsequent risk for developing MAC disease.

The mode of transmission is thought to be through inhalation, ingestion, or inoculation via the respiratory or gastrointestinal tract. Household or close contacts of those with MAC disease do not appear to be at increased risk for disease, and person-to-person transmission is unlikely.

In the absence of effective ART or chemoprophylaxis in those with AIDS-associated immunosuppression, the incidence of disseminated MAC disease is 20%–40% [81, 82]. For persons with a CD4+ count <100 cells/μL whom are receiving effective prophylaxis or have responded to ART with a sustained increase in CD4+ count to levels >100–200 cells/μL, the overall incidence has been estimated at 2 cases per 100 persons a year.

MAC disease typically occurs among persons with CD4+ counts <50 cells/μL. Other factors that are associated with increased susceptibility to MAC disease are high plasma HIV RNA levels (>100,000 copies/mL), previous OIs, previous colonization of the respiratory or gastrointestinal

tract with MAC, and reduced in vitro lymphoproliferative immune responses to M. avium antigens, possibly reflecting defects in T-cell repertoire.

2.4.6 Cytomegalovirus (CMV)

Before HAART, the prevalence of cytomegalovirus (CMV) disease in HIV patients with a $CD4^+$ count of <50 was 20% to 40%, and the incidence varied between 15 and 20 per 100 patient-years. Since the introduction of HAART, a more than fivefold decrease in the incidence of CMV disease has been reported by several authors [83]. Although CMV can cause colitis, pneumonitis, esophagitis, hepatitis, and neurologic disease, retinitis is the most common manifestation of active infection. CMV retinitis in HIV patients accounts for 75% to 85% of CMV end-organ disease. A recent investigation describing patients with CMV retinitis in the post-HAART era found a diverse demographic group with infection; most of them had received HAART; and as expected they had very low CD4 counts [84]. In addition, characteristics of the disease in this group were similar to those in the pre-HAART era.

2.4.7 Protozoal infections

Protozoal infections are the most common cause of diarrhea among HIV-infected patients. Opportunistic protozoans such as Cryptosporidium, Isospora belli, and Microsporidia are well-known GI pathogens. Other nonopportunistic protozoans such *as Giardia lamblia, E. histolytica, and Cyclospora cayetanensis* also cause disease [85].

Cryptosporidium, a coccidioidin protozoan with a life cycle that occurs entirely within a single host, can be transmitted from animals to humans by fecal water contamination or person-to-

person fecal–oral spread [86]. HIV-infected patients should be advised to wash their hands after contact with fecal material (e.g., changing diapers), exposure to pets, gardening, or contact with soil, and they should avoid oral–anal sexual practices. HIV-infected patients also should avoid drinking water from lakes and swallowing water during recreational activities. Outbreaks of cryptosporidiosis have been linked to municipal water supplies [87]. HIV-infected patients should avoid eating raw oysters because the oocysts can survive in oysters for >2 months [88]. In patients with AIDS, the frequency of chronic infectious diarrhea owing to cryptosporidiosis is 10% to 30% [86].

2.4.8 HIV associated malignancies

In addition to the OIs described under enteric infections, GI malignancy is common in patients with HIV. As the $CD4^+$ count declines, patients may develop Kaposi Sarcoma (KS), lymphoma, and invasive cervical cancer. The reason for the increased occurrence of malignancy is unknown, but it may be related to impaired immune function. In addition, effective antiretroviral therapy and prophylactic anti-infective therapy have extended the life span of patients with AIDS, increasing the likelihood that malignancies will be detected[89, 90].

Non Hodgkin Lymphoma (NHL) is more common than KS in people infected with HIV, particularly those with low $CD4^+$ counts (median, 100 cells/mm^3)[91].Unlike KS, NHL occurs in all risk groups of HIV-infected patients and does not predominantly occur in homosexual men[92]. High-grade NHLs account for approximately 3% of initial AIDS-defining illnesses in adults and adolescents [93]. The reason for the increased incidence is unknown; however, similar to KS, cytokine dysregulation may play a role [89].

2.5 Management and Access to medicines

According WHO, more than 5 million people are now receiving HIV treatment. In 2009 alone, 1.2 million people with HIV received ART for the first time-an increase in the number of people receiving treatment of 30% in a single year. Expanding access to treatment has contributed to a 19% decline in deaths among people living with HIV between 2004 and 2009 [1]. However, 10 million people living with HIV who are eligible for treatment under the new WHO guidelines are still in need [1]

Treatment coverage in low and middle income countries has reached more than 37, 45, and 50% in Sub-Sahara Africa, Caribbean and Latin America countries respectively [1].

However, despite the increasing coverage of ART, prophylaxis and management of opportunistic infections plays a very important role in the management of HIV/AIDS patients. OIs are still the leading cause of death in HIV/AIDS. Furthermore many patients in Africa start ART late, when their immune system has been severely damaged. This makes them very vulnerable to OIs. This is further complicated by the inability of the governments in these countries to put all eligible patients on ART due to economic constraints.

Management of opportunistic infections in Kenya is guided by the National manual for the management of HIV related opportunistic infections and conditions [94]. It aims at standardizing treatment of OIs and reduces chances of mismanagement. This is crucial because most HIV/AIDS patients are not managed by HIV specialists but by lower cadres of health professionals such as clinical officers and nurses. As a result, measuring the adherence of the healthcare workers to the national guidelines is an important indicator of the management of OIs.

2.6 Problem Statement

Prophylaxis for and management of OIs and the introduction of HAART have significantly decreased the incidence of AIDs related OIs and mortality in HIV- infected persons[95, 96, 97]. However, despite the availability of HAART in developing countries, OIs continue to cause considerable morbidity and mortality. The prevalence of OIs may vary in the different segments of the PLHA.

A review of incidence of HIV –related OIs between 1996 and 1998 in the United States found the incidence rates of esophageal candidiasis, tuberculosis, cryptosporidiosis, and chronic mucocutaneous herpes simplex virus disease were significantly higher among women, whereas Kaposi's sarcoma was more frequent among men [98].

In Kuala Lumpur Hospital, a retrospective review of 419 HIV/AIDS patients record showed that the prevalence of four major OIs were 48% ,13% ,11% and 7% for Tuberculosis, Pneumocystis pneumonia, toxoplasmosis and cryptococcal meningitis respectively. In addition, most of the patients were found to have CD_4 cell count less than 200 cells/mm^3 at the time of diagnosis [99].

A study that was done in India reported that parasitic infections were found in 35% HIV infected patients and low CD_4 cell count was significantly associated with opportunistic infections [100].

A cross-sectional study that was carried out in HIV-infected children at the KNH-CCC estimated the prevalence of OIs to be 14.3% [101]. However, another cross-sectional study carried out in Taita Taveta and Murang'a districts of Kenya, reported prevalence of 3.3% and 4.1 % respectively [102].

The above studies suggest there is a big variation in the reported prevalence of HIV/AIDS related opportunistic infections. Therefore further studies are needed to determine prevalence and spectrum of opportunistic infections at KNH-CCC

2. 7 Justification of the study

Since most of the Opportunistic infections known to affect HIV- infected patients are readily treatable and/ or preventable, with most of the treatment being simple, available and affordable, every effort should be made to facilitate proper management. However, there is need to establish local prevalence of these infections and evaluate appropriateness and accessibility of therapy given for their management.

It is hoped that, the findings of this study will contribute to informed, useful review of policy and operational decisions toward improving and strengthening care of HIV-infected adult patients.

Few studies on prevalence of OIs in Kenya have made it difficult to implement clinical strategies and programs to prevent their consequences and decrease cost of their management. OIs consume a large share of healthcare budget and significantly impair HIV/AIDS patients' quality of life, thus there is a great interest in identifying, and then remedying, predisposing factors that increase the risk of OIs.

Therefore, knowledge of the prevalence and management of opportunistic infections will guide in prioritizing of resources toward the most common opportunistic infections and support development of suitable intervention strategies to promote cost effective selection, procurement and rational use of medicines.

CHAPTER THREE

2.0 DESIGN AND METHODOLOGY

3.1 Study design

This was a hospital-based cross-sectional study conducted between July and August 2011. Patients visiting the CCC on the study dates were first seen by the attending clinician before their files were reviewed by the investigator. The files were reviewed for HIV related Opportunistic infections (OIs) recorded on the index visit only. OIs occurring on previous visits were not considered. The investigator was only interested in active or new OIs present on the index visit.

3.2 Study area description

The study was carried out at the Kenyatta National Hospital -Comprehensive Care Center (KNH-CCC). KNH is the largest public teaching and referral hospital in East Africa. The KNH-CCC is an outpatient clinic that serves as both a primary care center and a public referral center for HIV/AIDS patients from all over Kenya. Currently the center has more than 10,000 HIV infected patients enrolled and sees more than 100 patients daily.

3.3 Study population

Adults defined by age of 18 years and above infected with HIV/AIDs who visited the KNH-CCC during the course of the study.

3.4 Inclusion criteria

- Patients seen at KNH CCC during the study period.
- Patients' file with confirmatory HIV positive result.
- Adult defined by age of 18years and above.

3.5 Exclusion criteria

- *Files with history of HIV-exposure but no confirmatory HIV positive result.*
- Incomplete patient files with missing pages resulting in loss of information.
- Files of patient previously included/counted.

3.6 Sample size

From anecdotal information, the point prevalence of opportunistic infection in HIV-infected adult patient at KNH-CCC is estimated to be between 10 – 20 % (information obtained from Clinicians in KNH-CCC). Using this range, the estimated prevalence was assumed to be 15%. Also, a study carried out to determine the Prevalence of OIs in HIV-infected children at KNH CCC reported a prevalence of 14.3% [101]. Thus, the sample size for this study was calculated on the basis of a prevalence of 15%, at precision of 5% and a 95% level of confidence.

The Fischer et al formula for determining the minimum sample size was used [103]:

$n = Z^2 pq/ d^2$

Where

n= sample size

Z= 1.96 standard normal deviation at required confidence level

p= 0.15 Estimated prevalence or proportion

q= 1-p= 0.85

d=0.05 precision

n= [1.962 X 0.15 X 0.85]/ [0.052] = 196 patients' files

Hence, a minimum of 196 patient files was required

3.7 Data collection and analysis procedures

3.7.1 Variables

3.7.1.1 Dependent variable

The primary outcome of interest was proportion of HIV +ve adult patients who developed any of the following opportunistic infections:

- Bacterial infections (eg. Pulmonary tuberculosis, extrapulmonary tuberculosis , pulmonary and extrapulmonary tuberculosis , bacterial pneumonia , mycobacterium avium complex),
- Fungal infections (eg oral candidasis , esophageal candidiasis , Pneumocystis Jiroveci Pnemumonia , cryptococcal neuralagia Histoplasmosis, Penicillosis)
- Viral infections (eg Herpes infection, Hepatitis C virus infection, Hepatitis B virus infection, Oral hairy leukoplakia, Cytomegalovirus infection),
- Related parasitic (eg Cryptosporidiosis, Ectoparasites scabies, Toxoplasmic encephalitis)

The secondary outcomes of interest were factors associated with opportunistic infections in HIV infected patients. These included:

- CD_4 count
- Viral load
- WHO HIV stage
- Clinical treatment failure
- Patient's social behavior such as alcohol, smoking, Drug abuse.

The independent variable included the patients' demographics such as age and sex

3.7.2 Sampling methods

Incidental sampling was used to obtain the patients' files seen by clinicians during study period. The files were selected by simple random sampling and those meeting the inclusion criteria were reviewed for records of current opportunistic infections.

Deliberate efforts were made to get files of adults seen by different clinicians in the different rooms. These were randomly picked and reviewed by the investigator within the KNH-CCC premises. The investigator sat in the CCC reviewing the files of the patients soon after the patients were seen by the clinicians. This was done daily till the required sample size was achieved. A total of 333 patients' files were reviewed out of the total 1239 patients seen in the clinic during the study period. However, 22 files were eventually eliminated in the study due to failure to meet the inclusion criteria.

The files were reviewed for any active or new OI recorded on that day's visit. OIs occurring on earlier visits and not currently active were not considered. The data extracted from the files were entered into a pre-designed data collection form (appendix I).

3.7.3 Data Analysis Procedure

The data collected was transferred into Microsoft Access 2003 database and then analyzed using version 11.5 SPSS software. The level of significance was at 0.05 and P-value less than or equal to 0.05 was considered statistically significant.

3.7.4 Data Quality Control

The data collection tool was pretested by randomly sampling 50 patient files of HIV-infected adult seen at KNH-CCC. The tool was then adjusted and reformatted to facilitate effective and efficient data collection during the study. The data entered by an investigator into Microsoft Access 2003 database was thoroughly checked for accuracy and completeness. Errors and omissions identified were rectified.

On completion of data entry, data cleaning was carried out to correct any mistakes that might have occurred during data entry.

3.8 Ethical Considerations

3.8.1 Approval to carry out the study

Approval to carry out the study was sought from the Kenyatta National Hospital / University of Nairobi /Ethics and Research committee (Appendix IV).

3.8.2 Confidentiality

- The review of patient files was done within the KNH-CCC premises.
- All data obtained was kept under lock and key or in pass worded computer files to restrict access.
- Data forms did not bear patients' names or clinic numbers'. Patients were only identified by study numbers.
- A separate code list containing the study numbers and patients' clinic numbers' was maintained.

3.8. 3 Benefits from the Study

- The findings of the study will be communicated to the primary care givers which may help in improving quality of care of the HIV-infected adults in the future.

3.8.4 Risks involved

- There were no risks to the patients; there was no direct patient involvement in the study. Data was retrieved from files.

CHAPTER FOUR

4.0 RESULTS

4.1 Characteristics of the study participants

4.1.1 Selected demographic characteristics of the study participants

A total of 311 patient records retrieved from Kenyatta National Hospital-Comprehensive Care Centre (KNH-CCC) were considered for the study. **Table 4.1** presents selected demographic characteristics of the study participants. Mean age of the participants was 41 ± (9 SD) with a range of 21 and 74 years. A high proportion (42.8%) was aged between 35 and 44 years. Gender distribution was comparable, with a slightly high proportion of females (58.8%). Level of education varied from *non-formal education* to *university education*, with most of the participant (79.4%) attaining secondary education or lower.

Table 4.1: Selected demographic characteristics of the study participants

Variables	N=311	%
Age in years		
18 - 24	6	1.9
25 - 34	76	24.4
35 - 44	133	42.8
45 - 55	75	24.1
>55	21	6.8
Sex		
Male	128	41.2
Female	183	58.8
Marital status		
Single	73	23.5
Married	196	63.0
Divorced/Widowed	42	13.5
Education level		
</=Secondary	220	79.4
>Secondary	57	20.6
No response	34	
Occupation		
Unemployed	81	28.6
Employed	202	71.4
No response	28	

4.1.2 Participant's medical history

Assessment of patient's medical records revealed that most of the patients (55.3%) were diagnosed with HIV more than 36 months ago. After diagnosis, majority of the participants (84.2%) were immediately started on HAART while the rest were started at a later stage. At the start of therapy, 43.5% had CD4 cell count less than or equal to 200 cell/mm^3. A high proportion of the patients (35.1%) were initiated treatment at WHO stage III disease with the smallest (16.8%) being started at stage IV.

At the time of study, the most commonly used regimen was TDF based (52.3%) followed by AZT based regimens (26.6%). Current WHO stage in majority of the patients (81.0%) was I, with a smallest proportion being in stage II (4.5%) and IV (2.5%). A small proportion of the patients (21.8%) had CD4 cell count less than or equal to 200 cell/mm^3 by the time the study was conducted (**Table 4.2**).

Table 4.2: Participant's medical history

Variables	N=311	%
Duration since diagnosis in months		
0 - 12 months	64	20.6
13 - 24 months	37	11.9
25 - 36 months	38	12.2
>36 months	172	55.3
HAART started		
Yes	262	84.2
No	49	15.8
CD4 count (cells/mm3) when HAART started		
</= 200	131	43.5
>200	170	56.5
No response	10	
WHO stage when HIV was diagnosis		
I	73	25.6
II	64	22.5
III	100	35.1
IV	48	16.8
No response	26	
Duration being on HAART (Months)		
0 - 12 Months	47	15.1
13 - 24 Months	38	12.2
25 - 48 Months	70	22.5
>48 months	109	35.0
Not on HAART	47	15.1
Current HAART regimen base		
AZT based regimen	83	26.7
D4T based regimen	15	4.8
TDF based regimen	161	51.8
Other regimen	4	1.3
Not on HAART	48	15.4
Current WHO stage		
I	218	81.0
II	12	4.5
III	32	11.9
IV	7	2.6
No response	42	
Current CD4 count (cells/mm3)		
</= 200	54	21.8
>200	194	78.2
No response	63	

Out of 311 participants, 17.4% had at least one of the three factors commonly associated with opportunistic infections in HIV infected patients. **Figure 4.1** presents distribution of participants by factors known to predispose HIV infected patients to opportunistic infections.

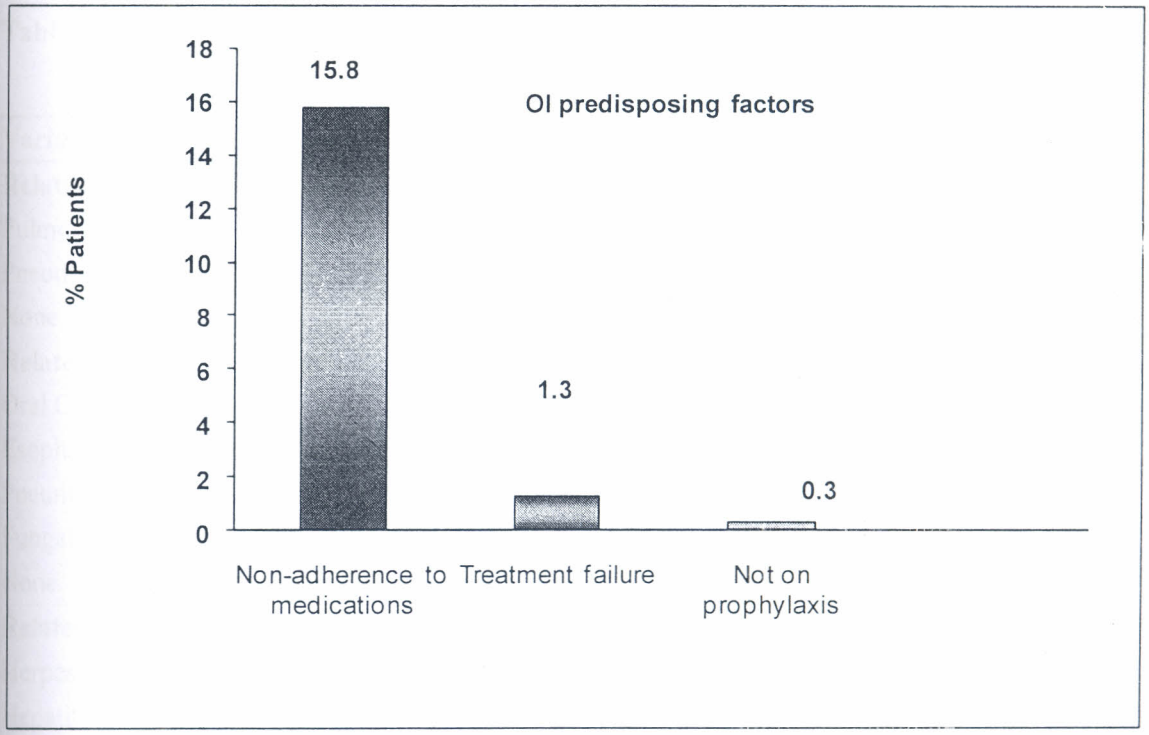

Figure 4.1: Factors predisposing HIV infected adult patients to develop OIs

A review of patient's current opportunistic infections was analysed as presented in **Table 4.3.** The most commonly reported bacterial infection was pneumonia (6.4%) where as pulmonary TB was reported by 3.9% of the participants. Among fungal infections, oral Candidiasis (0.6%) and fungal skin infection (0.6%) had the highest frequency of occurrence as reported by the

participants. Herpes infection (HSV and HZV) (0.6%) and Hepatitis C virus (0.3%) were the only reported viral infections. Only one patient (0.3%) suffered from parasitic related infection (warms). Malignancy related infections were observed in three patients; Kaposi sarcoma (0.6%) and Invasive carcinoma, cervix (0.3%). Others opportunistic infections included; wasting syndrome (0.3%) and diarrhoea (1.0%).

Table 4.3: Participants current opportunistic infections

Variables	N=311	%
Related bacterial infections		
Pulmonary TB	12	3.9
Pneumonia bacterial	20	6.4
None	280	90.0
Related fungal infections		
Oral Candidiasis	2	0.6
Esophageal Candidiasis	1	0.3
Pneumnocytis jiroeci pneumonia	1	0.3
Fungal skin infection	2	0.6
None	305	98.1
Related viral infections		
Herpes infection (HSV and HZV)	2	0.6
Hepatitis C virus infection	1	0.3
None	308	99.0
Related parasitic infections		
Warms	1	0.3
None	310	99.7
Related malignancy		
Kaposi sarcoma	2	0.6
Invasive carcinoma, cervix	1	0.3
None	308	99.0
Others opportunistic infections		
Wasting syndrome	1	0.3
Diarrhoea	3	1.0
None	307	98.7

An analysis of current opportunistic infection showed that 4 participants (1.3%) had 2 types of infections while the others 40 (12.9%) had only 1 type. This gave a cumulative prevalence of opportunistic infection of 14.1% (95% CI: 10.7 – 18.5), (**Figure 4.2**).

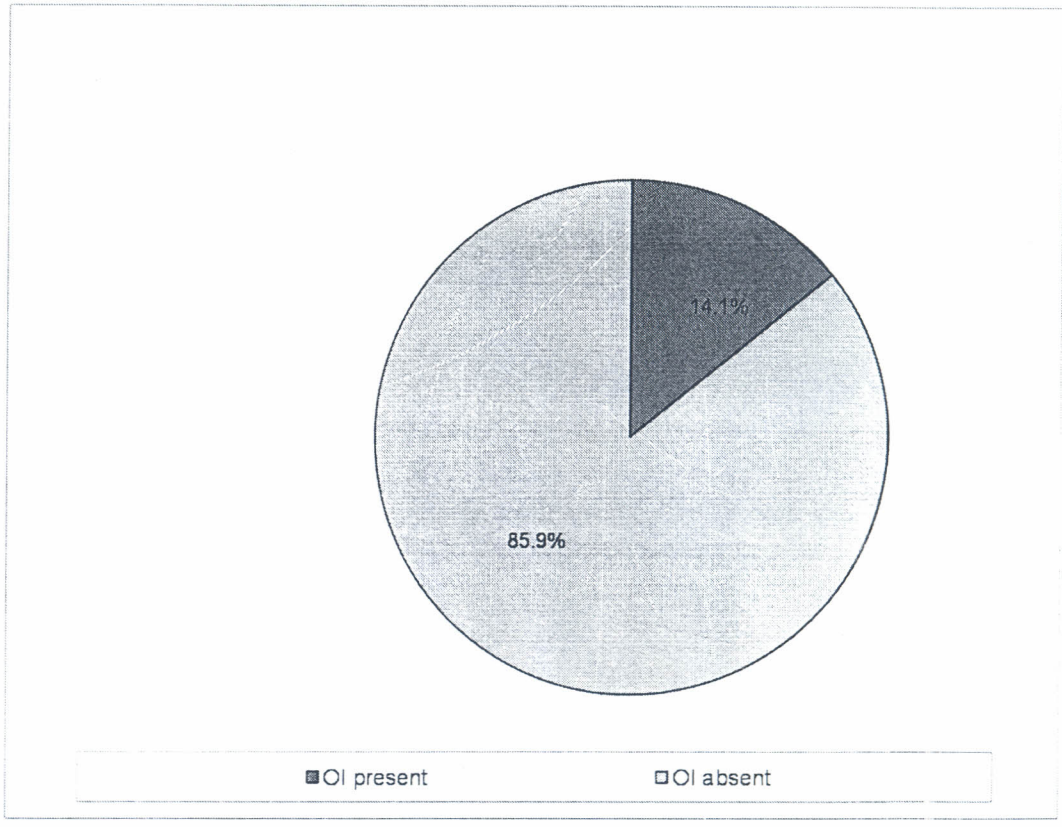

Figure 4. 2: Prevalence of current opportunistic infections

Opportunistic infections management compared to the Kenya National Manual for the management of HIV- related OIs and other Conditions. Worryingly, over 29 % of the OIs were not managed according to the Kenya National guideline. (**Figure 4.3**).

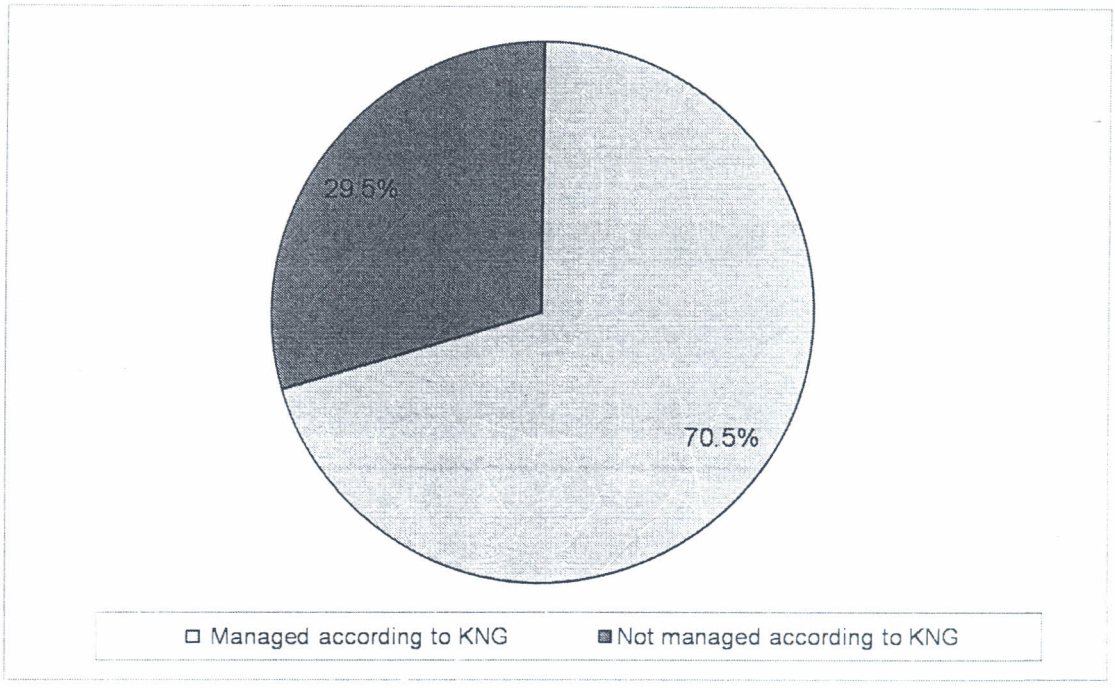

Figure 4.3: Opportunistic Infections management compared with Kenya National guidelines

4.1.3 Current Opportunistic infection in relation to ART regimen

The prevalence of OI was highest (20 %) among patient taking D4T based regimen **(Figure 4.4).**

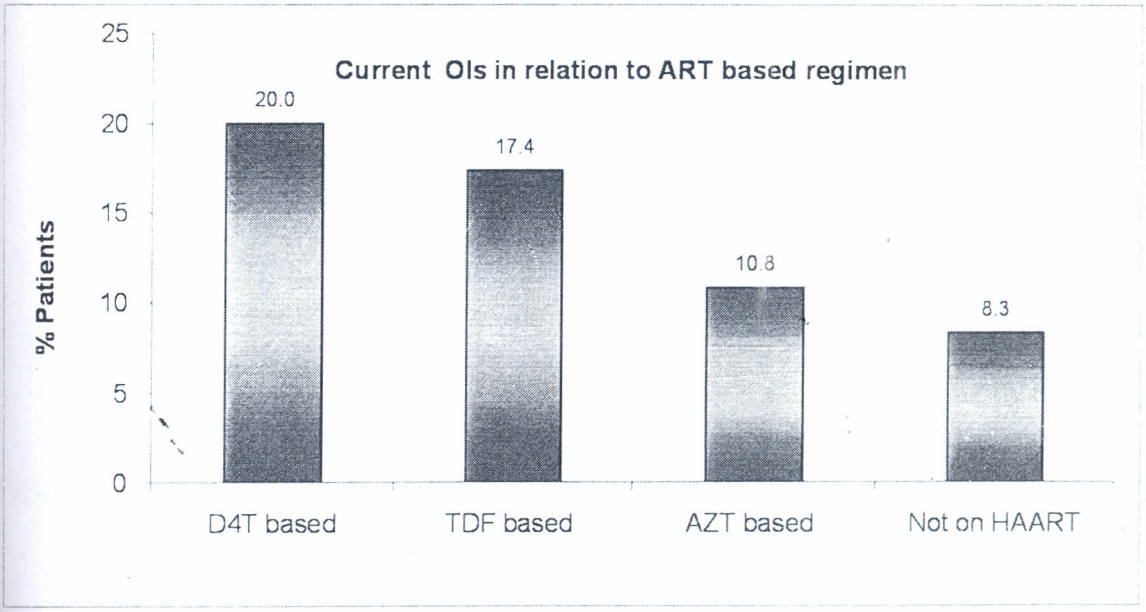

Figure 4.4: Current OIs in relation to antiretroviral therapy regimen

Figure 4.5 presents concurrent medications being taken in addition to ARTs by 94.2% of the participants. The majority (90%) of patients were on Co-trimoxazole.

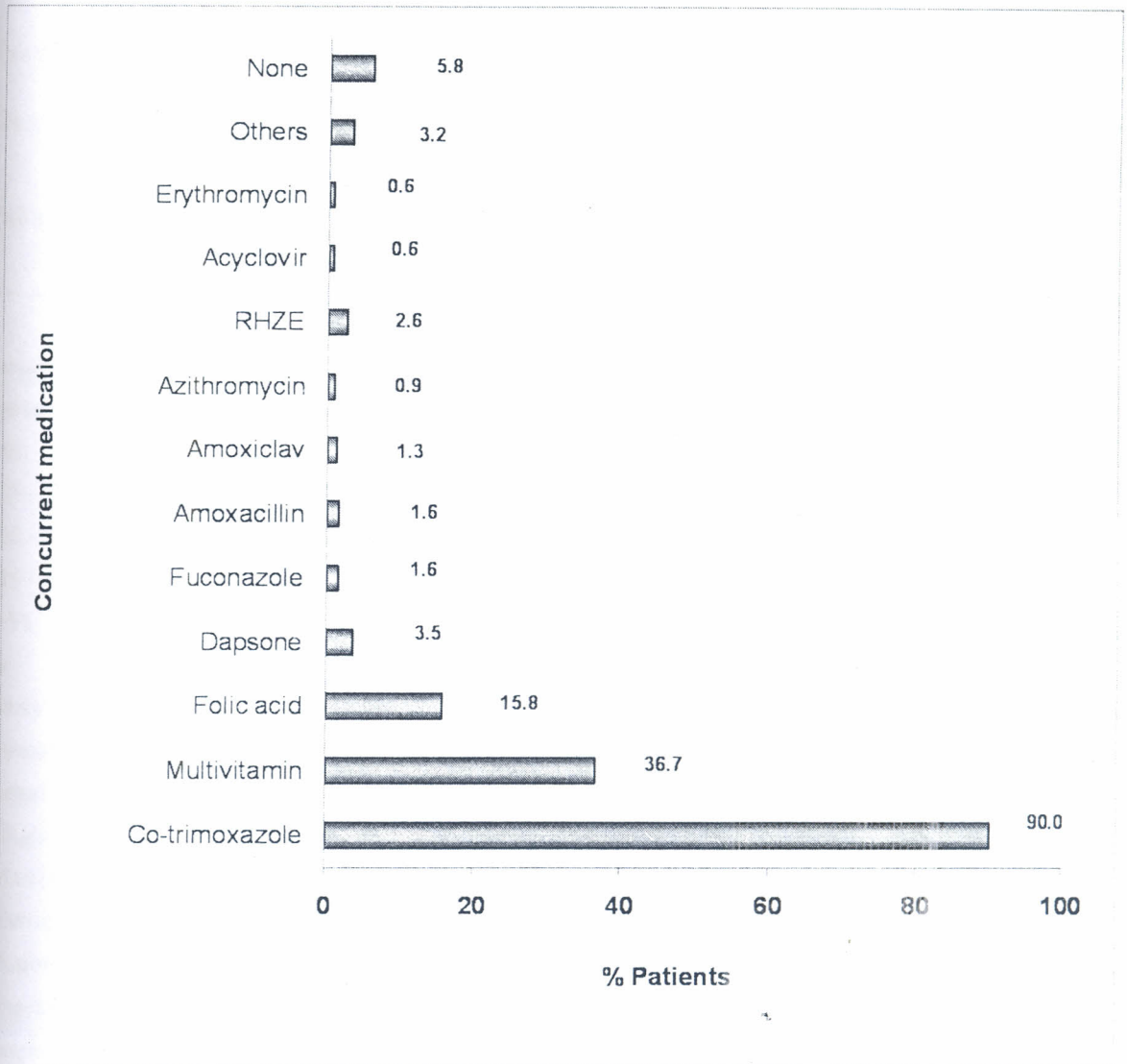

Figure 4.5: Concurrent medication being taken by patients a part from ARTs

4.2 Bivariate analysis

4.2.1 Relationship between current opportunistic infection status and selected demographic characteristics

Relationship between current Opportunistic infection status and selected demographic characteristics was analysed as presented in **Tables 4.4**. None of the factors was significantly associated with current opportunistic infection status (P>0.05).

Table 4.4: Current OI status in relation to selected demographic characteristics

	Present (n=44)		Absent (n=267)			95% CI		
Variables	n	%	n	%	OR	Lower	Upper	P value
Age in years								
18 – 24	0	0.0	6	100.0	UD	UD	UD	0.999
25 – 34	13	17.1	63	82.9	0.88	0.25	3.04	0.836
35 – 44	19	14.3	114	85.7	0.71	0.21	2.33	0.571
45 – 55	8	10.7	67	89.3	0.51	0.14	1.89	0.311
>55	4	19.0	17	81.0	Reference			
Sex								
Male	16	12.5	112	87.5	0.79	0.41	1.53	0.486
Female	28	15.3	155	84.7	Reference			
Marital status								
Single	11	15.1	62	84.9	1.31	0.42	4.08	0.638
Married	28	14.3	168	85.7	1.23	0.45	3.41	0.686
Divorced/Widowed	5	11.9	37	88.1	Reference			
Occupation								
Unemployed	12	14.8	69	85.2	1.13	0.54	2.35	0.749
Employed	27	13.4	175	86.6	Reference			
No response	5		23					
Education level								
</=Secondary	30	13.6	190	86.4	1.13	0.47	2.72	0.789
>Secondary	7	12.3	50	87.7	Reference			
No response	7		27					

UD-Undefined

4.2.2 Relationship between current opportunistic infection status and patient's medical history

Four out of ten factors on patient's medical history were significantly associated with current opportunistic infection status (P<0.05) as shown in **Table 4.5**.

Duration since HIV was diagnosed of less than or equal to 12 months was marginally associated with current opportunistic infection (P= 0.05). A high proportion of opportunistic infection was observed among participants with less than or equal to 12 months duration since HIV was diagnosed (20.3%) compared to those with more than 36 months (10.5%). A patient with less than or equal to 12 months duration since diagnosis of HIV was 2.18 [95% CI = 1.00 – 4.76] times more likely to develop opportunistic infection compared to one with more than 36 months.

Also, WHO clinical stage III or IV when HIV was diagnosed was marginally associated with current opportunistic infection, (P=0.05). There was high proportion of opportunistic infection among participants in WHO clinical stage III or IV of the disease (20.3%) compared to those in stage I (9.6%). A patient in stage III or IV was 2.40 [95% CI = 1.00 – 5.76] times more likely to develop opportunistic infection compared to one in stage I.

Less than or equal to 12 months duration on HAART was significantly associated with current opportunistic infection (P=0.018). A high proportion of opportunistic infection was observed among participants with less than or equal to 12 months duration (25.5%) compared to those not

on HAART (6.4%). A patient with duration on HAART of less than or equal to 12 months was 5.03 [95% CI = 1.32 – 19.22] times more likely to develop opportunistic infection compared to one not on HAART.

Current CD4 count ≤200 cells/mm^3 was significant associated with opportunistic infection. (P=0.044). There was high proportion of opportunistic infection among participants with CD4 count ≤200 cells/mm^3 (24.1%) compared to those with CD4 count >200 cells/mm^3 (12.9%). A patient with CD4 count ≤200 cells/mm^3 was 2.14 [95% CI = 1.01 – 4.55] times more likely to develop opportunistic infection compared to one with CD4 count >200 cells/mm^3.

Table 4.5: Current OI status in relation to participant's medical history

	Present (n=44)		Absent (n=267)			95% CI		
Variables	**n**	**%**	**n**	**%**	**OR**	**Lower**	**Upper**	**P value**
Duration since diagnosis in months								
</=12 months	13	20.3	51	79.7	2.18	1.00	4.76	**0.050**
13 - 36 months	13	17.3	62	82.7	1.79	0.83	3.88	0.138
>36 months	18	10.5	154	89.5	Reference			
WHO stage when HIV was diagnosed								
III or IV	30	20.3	118	79.7	2.40	1.00	5.76	**0.050**
II	4	6.3	60	93.8	0.63	0.18	2.25	0.476
I	7	9.6	66	90.4	Reference			
No response	3		23					
HARRT started								
Yes	40	15.3	222	84.7	2.03	0.69	5.95	0.190
No	4	8.2	45	91.8	Reference			
CD4 count (cells/mm3) when HAART started								
</=200	23	17.6	108	82.4	1.51	0.80	2.87	0.205
>200	21	12.4	149	87.6	Reference			
No response	0		10					
Duration being on HAART (Months)								
0 - 12 Months	12	25.5	35	74.5	5.03	1.32	19.22	**0.018**
13 - 24 Months	6	15.8	32	84.2	2.75	0.64	11.83	0.174
25 - 48 Months	10	14.3	60	85.7	2.44	0.64	9.41	0.194
>48 months	13	11.9	96	88.1	1.99	0.54	7.32	0.303
Not on HAART	3	6.4	44	93.6	Reference			
Current HAART regimen code								
D4T based regimen	3	20.0	12	80.0	2.06	0.49	8.69	0.327
TDF based regimen	28	17.4	133	82.6	1.73	0.78	3.86	0.180
Other regimen	0	0.0	4	100.0	UD	UD	UD	0.999
Not on HAART	4	8.3	44	91.7	0.75	0.22	2.57	0.644
AZT based regimen	9	10.8	74	89.2	Reference			
Current WHO stage								
III or IV	39	100.0	0	0.0	UD	UD	UD	0.997
II	5	41.7	7	58.3	Reference			
I	0	0.0	218	100.0	UD	UD	UD	0.994
No response	0		42					
Current CD4 count (cells/mm3)								
</=200	13	24.1	41	75.9	2.14	1.01	4.55	**0.044**
>200	25	12.9	169	87.1	Reference			
No response	6		57					
Predisposing factors								
Yes	9	16.7	45	83.3	1.27	0.57	2.82	0.559
No	35	13.6	222	86.4	Reference			
Substance use								
Yes	7	13.5	45	86.5	0.87	0.33	2.25	0.767
No	16	15.2	89	84.8	Reference			
No response	21		133					

4.3 Multivariate analysis

Multivariate analysis was performed to identify independent predictor(s) of current state of opportunistic infection among adult patients diagnosed with HIV. Four factors associated with current opportunistic infections status at P<0.1 during bivariate analysis were considered for multivariate analysis. These include; (1) Duration since HIV diagnosis (months), (2) WHO clinical stage of disease when HIV was diagnosed, (3) Duration being on HAART (months) and (4) Current CD4 count. Upon fitting the factors using Binary logistic regression and specifying *'backward conditional'* method with removal at P<0.05, two factors were retained in the final model as shown in **Table 4.6**.

Table 4.6: Predictors of current opportunistic infection

		95.0% CI		
Predictor variables	**AOR**	**Lower**	**Upper**	**P value**
Duration since diagnosis (months)				
</=12 months	3.89	1.58	9.59	**0.003**
13 - 36 months	2.21	0.90	5.40	0.083
>36 months	Reference			
WHO stage when HIV was diagnosed				
III or IV	3.79	1.43	10.03	**0.007**
II	0.51	0.12	2.18	0.364
I	Reference			

From the results it appears that the association of current opportunistic infection status and (1) Duration being on HAART (months), (2) Current CD4 count were being confounded by duration since HIV diagnosis in months and/or WHO clinical stage when HIV was diagnosed. After fitting all the four factors together, variance of opportunistic infection due to duration being on HAART (months) and current WHO clinical stage was less than the variance of opportunistic infection due to duration since HIV diagnosis (months) and WHO clinical stage when HIV was diagnosed, there by rendering the two factors (Duration being on HAART (months) and Current WHO disease stage) statistically insignificant and therefore removing them from the model. Duration since HIV diagnosis (months) and WHO clinical stage when HIV was diagnosed were therefore retained in the final model.

Adjusting for duration since HIV diagnosis (months), WHO clinical staging of disease III or IV was significantly associated with current opportunistic infection (AOR= 3.79 [95% CI = 1.43 – 10.03], P=0.007). A patient in stage III or IV when HIV was diagnosed has 3.79-folds risk of having opportunistic infection compared to one in stage I.

Similarly, adjusting for WHO clinical stage of disease when HIV was diagnosed, less than or equal to 12 months duration since diagnosis was significantly associated with current opportunistic infection (AOR= 3.89 [95% CI = 1.58 – 9.59], P=0.003). A patient with less than or equal to 12 months duration since HIV diagnosis has 3.89-folds risk of having opportunistic infection compared to one with more than 36 months.

CHAPTER FIVE

5.0 DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 DISCUSSION

5.1.1 Prevalence of Opportunistic infections

The main objective of this study was to establish the prevalence of opportunistic infections in HIV- infected, adult patients at KNH-CCC and evaluate their management in regard to Kenya National Manual for the Management of HIV- related Opportunistic Infections and other Conditions.

Three hundred and eleven adult patients infected with HIV were included in this study: in whom forty-four (14.1%) patients had opportunistic infections during the study period. Out of the 44, 4 participants (1.3%) had 2 types of infections while the other 40 (12.9%) had 1 type bringing the prevalence of opportunistic infections to 14.1 % (95% CI: 10.7-18.5).

This finding is lower than the initial anecdotal estimate of 15% prevalence of opportunistic infections. So this difference may not represent a true reduction in infections prevalence as the initial estimate was based on a study that was carried out in children and anecdotal information obtained from Clinicians at KNH-CCC, which may have been over estimated. In addition, the difference between our finding and information obtained from clinician at KNH-CCC study may be attributed to the fact that our study was interested only in opportunistic infections that were

active or diagnosed on the days of data collection. Therefore, any opportunistic infections which were not confirmed the same day may likely have been missed.

Also OIs which required laboratory confirmation may have been missed since some investigations required several days before results come back to confirm the diagnosis.

Our finding is almost similar to the finding of cross-sectional study that was carried out in children infected with HIV at KNH –CCC which estimated the prevalence of OIs in children to be 14.3 % [101].

However, it is expected that there should be a reduction in opportunistic infections prevalence among HIV-infected adults following initiation of antiretroviral therapy and chemoprophylaxis [95-97]. For instance, a randomized controlled trial using Co-trimoxazole has documented that chemoprophylaxis can reduce incidence of opportunistic infections [33-37]. Moreover, many serious opportunistic infections such as *cryptococcocal* meningitis and toxoplamosis are directly reported to KNH and admitted in the wards rather than an outpatient clinic of CCC. Therefore, we may have missed some cases of Opportunistic infections. This could explain why this study failed to capture any of the serious OIs such as *cryptococcocal* meningitis.

The finding of this study is much higher than the finding of cross-sectional studies that were carried out in Murang'a and Taita Taveta, which estimated the prevalence of OIs to be 4.1% and 3.3 % respectively [102]. This high difference in the prevalence may be attributed to geographical and population density variations between Nairobi, Murang'a and Taita Taveta. It may also be because; KNH being a referral hospital may have received more seriously ill patients than the district hospitals of Murang'a and Taita Taveta.

The most common opportunistic infections reported in this study were bacterial pneumonia, pulmonary tuberculosis, diarrhoea, fungal skin infections, Candidiasis (oral and esophageal) wasting syndrome, herpes (HSV and HZV), kaposi sarcoma and hepatitis C Virus. Bacterial pneumonia was the most frequent opportunistic infection, reported in 6.4 % patients. However, in retrospective review of a Cohort of HIV infected patients from 1984 to 2008 at American University Based Medical Center in Lebanon, cerebral toxoplasmosis 21% was the most frequently reported OIs followed by fungal infections 17%. [38].

Our data showed that pulmonary tuberculosis and diarrhoea were the second leading opportunistic infections and with a prevalence of 3.9% and 1% patients respectively. However, worldwide, tuberculosis is the most common cause of death among patients with AIDs [69]. This finding is contrary to the finding of Kuala Lumpur hospital based study that estimated prevalence of tuberculosis to be 48% [98]. But Kuala Lumpur hospital based study was retrospective review of HIV infected cohort form 1994 to 2001.

In South Africa, one out of six patients (16%) who had no symptoms of tuberculosis at the time of diagnosis screening actually had positive sputum culture for TB [107]. Even adding chest X-ray, Clinicians may still miss many cases, because the X-ray of HIV- infected TB patients can be normal(20 – 30% of times) especially in cases of Advanced AIDS [108].In addition , 9% (1 of every 11patients) randomly selected HIV infected patients living in community had TB [107] but more than 50% of these had not been diagnosed due to the lack of typical symptoms

suggestive of pulmonary tuberculosis and this may explain why so many patients are not diagnosed in clinic.

In Kenya, 2 out of 3 (64%) of HIV-infected TB patients are more likely to be missed, when microscope only was used as standard diagnostic tools. HIV-infected TB patients with culture–confirmed TB were Acid Fast Bacilli smear negative [109]. In addition, based on traditional understanding of HIV –negative Tuberculosis, standard screening approaches rely on symptoms of cough for more than 2-3 weeks in order to identify pulmonary TB suspect [110]. However, in HIV clinic in South African, relying only on cough missed 50% of pulmonary TB cases.

Furthermore, tuberculosis diagnosis requires several days before definite and objective diagnosis is confirmed. Therefore, there is possibility that some tuberculosis cases may have been missed during the study period or referred to TB clinic. however, this finding is more than 3 fold the finding of WHO Global surveillance and monitoring project which reported the rate of TB-HIV co-infections exceed 1 per 100 population in some areas of Sub-Sahara Africa [6].

Others OIs included 0.6% patients with the following; skin fungal infections, oral Candidiasis and herpes (HSV and HZV) and 0.3% patients with wasting syndrome, PCP, esophageal Candidiasis, and hepatitis C virus. However, one study showed that esophageal Candidiasis was the first opportunistic infection in 3% to 10% of HIV-infected patients and is the second most common AIDS-defining disease after *Pneumocystis jiroveci* pneumonia and the mean incidence of esophageal candidiasis among HIV-infected patients was less than Oropharyngeal candidiasis (OPC), and ranges from 15% to 20% [104]. Our study finding may present true reduction in the prevalence of Candidiasis compared to AMUBC study in Lebanon which was carried out in

period between pre and post highly active antiretroviral therapy [38]. In addition, to the widespread use of Azoles prophylaxis in those patients who had Cryptococcal meningitis and maintained on it until the CD4 increases to more 200cells/mm3 and sustained for period of 6 months.

Interestingly, Kaposi sarcoma was among the forth commonly reported opportunistic infection by 0.6% of patients. However, observational cohort of HIV infected adult with AIDS –associated Kaposi's sarcoma in South Africa estimated the prevalence of KS to be 3.6% [111]. This difference may be explained by the fact that our study was interested in active OIs during the study period. Furthermore, South African study was observation cohort of HIV infected adults from 2001 to 2007.

The study found that, there was significant association between study population's current OIs and WHO stage when HIV was diagnosed (P= 0.007). There was high proportion of opportunistic infection among participants in WHO stage III or IV of the disease (20.3%) compared to those in stage I (9.6%). The proportion of OI among participants in stage II (6.3%) was less than those in stage I. A patient in stage III or IV was 3.79 [95% CI: 1.43-10.03] times more likely to develop opportunistic infection compared to one in stage I. These finding supports the fact that majority of patients are unaware of their HIV infection and seek medical care when OIs became initial indicator of their disease [10, 15, 16]. Since certain OIs are associated with reversible increases in circulating Viral load [26-31], and these increases could lead to accelerated progression or transmission of HIV [32].Therefore, a lot of effort are need to enhance and encourage early detection of asymptomatic HIV-infected patients and providing them with timely antiretroviral therapy and appropriate chemoprophylaxis against specific OIs would

decrease morbidity, mortality, and improve the quality of life of HIV-infected patients in this country.

In addition, expanded awareness campaigns targeting the general population regarding HIV voluntary counseling and testing which may help in identifying HIV cases in early stage, before profound immune destruction become inevitable.

Similarly, adjusting for WHO clinical stage when HIV was diagnosed, less than or equal to 12 months duration since diagnosis was significantly associated with current opportunistic infection (AOR= 3.89 [95% CI = 1.58 – 9.59], P=0.003). A patient with less than or equal to 12 months duration since HIV diagnosis has 3.89-folds risk of having opportunistic infection compared to one with more than 36 months.

Analysis of CD4 count (cells/mm3) when HAART was started revealed important findings. Although the significance was arrived at (P=0.04). However, the CD4 count it was being cofounded by the by duration since HIV diagnosis. There was high proportion of opportunistic infections among participants with CD4 count ≤200 cells/mm^3 (24.1%) compared to those with CD4 count >200 cells/mm^3 (12.9%). A patient with CD4 count ≤200 cells/mm^3 was 2.14 [95% CI = 1.01 – 4.55] times more likely to develop opportunistic infection compared to one with CD4 count >200 cells/mm^3. Our finding is in line with various studies which documented that massive destruction of immune system occurs when the CD4 count is less 200 cells/mm^3 and increases the risk for OIs [39, 41, 42, 43].

5.1.2 Management of Opportunistic infections

Out of the 44 patients with at least one opportunistic infection, 29.5 % were not managed according to the *Kenya National Manual for the management of HIV-related Opportunistic infections and other conditions*. OIs have been the principle cause of morbidity and mortality in people living with HIV and AIDS [7]. However, in the early 1990s, the use of HAART, chemoprophylaxis and better strategy for management of OIs contributed to improved quality of life and survival by reducing OIs related mortality [7-14]. Hence, a lot of effort is needed to reinforce adherence of health care providers to National Manual for the management of HIV-related OIs and other Conditions which is the better strategy to improve quality of life and survival.

Standardization of OIs management by the guidelines help the patients seen by the lower cadres of health personnel, who are the majority, to receive the same quality of care as those seen by the HIV specialists in Kenya. The guidelines also help in monitoring and evaluating the management of OIs in the country. As such, they may be used to inform the review of the guidelines.

The most commonly used concurrent medication for management of OIs was RHZE (2.6%), fluconazole (1.6%) and amoxicillin (1.6%) of the patients for management of pulmonary tuberculosis, fungal infections and bacterial pneumonia respectively.

In this study, the most commonly used medication by participants as chemoprophylaxis was Co-trimoxazole. It was used by 90% of the patients. This is much higher than the 12.1% which was

reported by Kenya AIDs indicatory Survey (KAIS) 2007 [105].This may indicate a good compliance by KNH-CCC healthcare providers with the national guidelines which recommend putting all HIV patients on Co-trimoxazole. This may also suggest that significant progress has been made in terms of chemoprophylaxis coverage in the country since the KAIS which will improve quality of life and survival.

This is supported by the, Development of Anti-Retroviral Therapy in Africa trial (DART) which showed that Co-trimoxazole prophylaxis reduced overall mortality risk by 35% (OR 0.65, [0.50–0.85], p=0·001) compared to those who were not on prophylaxis. However, there was variation in mortality reduction with time: with greatest mortality reduction occurring within the first 12 weeks of treatment, sustained from 12–72 weeks and no evident afterward [106].

5.2 STUDY LIMITATIONS

Our study was limited by reliance on empirical clinician's diagnosis of opportunistic infections. Laboratory results were not readily available. This may lead to underestimation of OIs. Certain infections such as tuberculosis required at least more than three days for the diagnosis to be confirmed, therefore, if the diagnosis was not confirmed on the day of data collection, it was missed as an OI.

Serious opportunistic infections were usually referred to KNH wards or specialized clinics within KNH such as the TB Clinic; therefore we may have missed some of the Opportunistic infections.

Also in some cases, the study was underpowered by a number of no responses due to missing variables such as current CD4 count in many patients' files.

5.3 CONCLUSION

The overall prevalence of opportunistic infections was 14.1%. Bacterial Pneumonia and pulmonary tuberculosis were the most commonly observed opportunistic infections during the study period.

Co-trimoxazole chemoprophylaxis was used by more than 90% of the patients, indicating a high adherence by the health workers to the national OIs prophylaxis recommendations. However, more than 29% of opportunistic infections were not managed according to the *Kenya National Manual for the management of OIs and related Conditions.*

5.4 RECOMMENDATIONS

Continuous monitoring and evaluation of opportunistic infections should be done to reduce the high burden they are putting on HIV/AIDS patients. Adherence of health care providers to Kenya National Guidelines on management of OIs should also be reinforced.

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APPENDICES

APPENDIX1: DATA COLLECTION FORM

Study No: P 148/04/2011 **Date: DD.MM [ ] [ ] [2011]**

Serial No :..... **Data collector initial:.....**

SECTION A: PATIENT BIODATA

1. **Patient code No: [.....]**
2. **Date of birth: DD,MM,YYYY [.] [.] [. . .]**
3. **Age: [ ] years**
4. **Sex**
   A. Male [1]
   B. Female [2]
5. **Residence:** .....
6. **Marital status**
   A. Single [1]
   B. Married [2]
   C. Divorced [3]
   D. Widowed [4]

7. **Occupation:**

A. Unemployed [1]

B. NGOs [2]

C. Self employed [3]

D. Government employee [4]

E. Student [5]

8. **Patient's Social behavior:**

A. None [1]

B. Drink alcohol heavily [2]

C. Drink occasionally [3]

D. Drug abuse [4]

E. B & D [5]

F. C & [6]

9. **Date of HIV diagnosis DD MM YYYY [.] [.] [. . .]**

10. **WHO stage when HIV was diagnosis**

A. I [1]
B. II [2]
C. III [3]
D. IV [4]
E. NR [5]

11. HAART started

A. Yes [1]
B. No [2]

12. HAART regimen code [.]

13. **CD4 count (cells/mm3) when HARRT started** [.....cells/ul], if no value available – 99 [ ]

14. Duration being on HAART(Months) [ ]

A. 0 -12 [1]
B. 13- 24 [2]
C. 25- 48 [3]
D. 49-60 [4]
E. > 60 [5]
F. Not on HAART [6]

SECTION B: CURRENT OIs (Please record only OIs which has been diagnosis on the day of data collection)

15. Current WHO stage:

A. I [1]
B. II [2]
C. III [3]
D. IV [4]
E. NR [5]

16. Current CD4 count (cells/mm3) [.....cells/ul], if no value – 99 [ ]

17. Viral load where available .....copies/ ul , if no value -99 [ ]

18. Related bacterial infections

CODE	OIs	YES [1]	NO [2]
A	None		
B	Pulmonary Tuberculosis		
C	Extrapulmonary tuberculosis		
D	Pulmonary and extrapulmonary TB		
E	Pneumonia bacterial		
F	Mycobacterium avium complex infection		
G	Other Specify		

19. Related fungal infections

CODE	OIs	YES [1]	NO [2]
A	None		
B	Oral Candidiasis		
C	Esophageal Candidiasis		
D	Pneumnocytis jiroeci pneumonia		
E	Cryptococcal meningitis		
F	Histoplasmosis		
G	Penicillosis		
H	Others , specify		

20. Related viral infections

CODE	OIs	YES [1]	NO [2]
A	None		
B	Herpes infection (HSV and HZV)		
C	Hepatitis C virus infection		
D	Hepatitis B virus infection		
E	Oral hairy leukoplakia		
F	Cytomegalovirus infection		
G	Others, specify		

21. Related parasitic infections

CODE	OIs	YES [1]	NO [2]
A	None		
B	Cryptosporidiosis		
C	Ectoparasites scabies		
D	Toxoplasmic encephalitis		
E	Cryptosporidiosis		
F	Others, specify		

22. Related malignancy

CODE	OIs	YES [1]	NO [2]
A	None		
B	Kaposi sarcoma		
C	Non Hodgkin's lymphoma		
D	Invasive carcinoma, cervix		
E	Others, specify		

23. Others opportunistic infections

CODE	OIs	YES [1]	NO [2]
A	None		
B	Wasting syndrome		
C	AIDS dementia		
D	Diarrhea		
E	HIV encephalopathy		
F	Others, specify		

24. Risk factors predisposing HIV infected adult patients to develop OIs

CODE	OIs	YES [1]	NO [2]
A	None		
B	Clinical failure		
C	Non adherence to medications		
D	Not on prophylaxis		
E	Diagnosed when OI has already occurred		

25. Concurrent medication being by patients a part from ARTs

CODE	OIs	YES [1]	NO [2]
A	None		
B	Acyclovir		
C	Amphotricin B		
D	Clindamycin		
E	Co-trimoxazole		
F	Dapsone		
G	Flucytosine		
H	Folic acid		
I	Forscarnet		
J	Fuconazole		
K	Ganciclovir		
L	Irion supplement		
M	Multivitamin		
N	Pyrimethamine		
O	RH		
P	RHE		
Q	RHZE		
R	RHZES		
S	Sulfadiazine		
T	Valgabciclovir		
U	Other specify		

26. OIs management with Kenya National guideline

A. Yes [1] B. No [2]

NUMBER CODES USED FOR THE ART REGIMENS IN THE STUDY

NO	REGIMEN
1	3TC, ABC, LPV/r
2	3TC, NVP, Nelfinavir (Viracpt)
3	ABC, 3TC, EFV
4	ABC, 3TC, EFV
5	AZT, 3TC, ABC
6	AZT, 3TC, EFV
7	AZT, 3TC, NVP
8	AZT, 3TC. LPV/r
9	AZT,3TC, Indinavir
10	D4T, 3TC ,Idinavir (Crixivan)
11	D4T, 3TC, EVF
12	D4T, 3TC, LPV/r
13	D4T, 3TC, NVP
14	D4T, DDI, EVF
15	D4T, DDI, LPV/r
16	DDI, 3TC, EFV.
17	DDI, 3TC, NVP
18	DDI, ABC, LPV/r
19	DDI, AZT, LPV/r
20	DDI, AZT, NFV
21	DDI, D4T, NVP
22	TDF, 3TC, EFV
23	TDF, 3TC, LPV/r
24	TDF, 3TC, NVP
25	TDF, ABC, LPV/r
26	TDF, DDI, LPV/r
27	Not on HARRT
28	TDF, 3TC , ABC

APPENDIXII: SAMPLING FORM

STUDY NUMBER	IP NUMBER	STUDY NUMBER	IP NUMBER
001		021	
002		022	
003		023	
004		024	
005		025	
006		026	
007		027	
008		028	
009		029	
010		030	
011		031	
012		032	
013		033	
014		034	
015		035	
016		036	
017		037	
018		038	
019		039	
020		040	

APPENDIX III: FILE EXCLUSION FORM

PATIENT CLINIC NUMBER	REASON FOR EXCLUSION	PATIENT CLINIC NUMBER	REASON FOR EXCLUSION

APPENDIX IV: KNH & UON – ERC APPROVAL LETTER

KENYATTA NATIONAL HOSPITAL
Hospital Rd. along, Ngong Rd.
P.O. Box 20723, Nairobi.
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP", Nairobi.
Email: KNHplan@Ken.Healthnet.org

Ref: KNH-ERC/ A/161

5th July 2011

Dr. Francis Marcello Malwal
Dept. of Pharmaceutics & Pharmacy Practice
School of Pharmacy
University of Nairobi

Dear Dr. Malwal

Research Proposal: "Prevalence and Management of opportunistic infections in HIV-infected Adult patients at Kenyatta National Hospital" (P148/04/2011)

This is to inform you that the KNH/UON-Ethics & Research Committee has reviewed and **approved** your above revised research proposal . The approval periods are 5th July 2011 4th July 2012.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimens must also be obtained from KNH/UON-Ethics & Research Committee for each batch.

On behalf of the Committee, I wish you a fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of the data base that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

PROF A N GUANTAI
SECRETARY, KNH/UON-ERC

c.c. The Deputy Director CS, KNH
The Dean, School of Pharmacy, UON
The Chairman, Dept.of Pharmaceutics & Pharmacy Practice, UON
The HOD, Records, KNH
Supervisors: Prof. G. Muriuki, Dept.of Pharmacology & Pharmacognosy, UON
Dr. Shital Maru, Dept.of Pharmaceutics & Pharmacy Practice, UON
Dr. E.M. Mwangangi, Dept. of Pharmaceutics & Pharmacy Practice, UON

APPENDIX V: WHO CLINICAL STAGING OF HIV FOR ADULTS & ADOLESCENTS WITH CONFIRMED INFECTION

Stage I	▪ Asymptomatic ▪ Persistent generalized lymphadenopathy
Stage II	▪ Moderate unexplained weight loss (< 10% of presumed or measured body weight) ▪ Recurrent respiratory infections (Sinusitis, tonsillitis, otitis media, and pharyngitis) ▪ Herpes zoster ▪ Angular cheilitis ▪ Recurrent oral ulceration ▪ Seborrheic dermatitis ▪ Fungal nail infections
Stage III	▪ Unexplained severe weight loss (> 10% of presumed or measured body weight) ▪ Unexplained chronic diarrhea for > 1 month ▪ Unexplained persistent fever for > 1 month (. 37.6º C, intermittent or constant) ▪ Persistent oral candidiasis (thrush) ▪ Oral hairy leukoplakia ▪ Pulmonary tuberculosis (current) ▪ Severe presumed bacterial infections (eg, pneumonia, empyema, pyomyositis, bone or joint infections. meningitis, bacteremia) ▪ Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis ▪ Unexplained anemia (hemoglobin <8 g/dL) ▪ Nutropenia (neutrophils <500cells/uL) ▪ Chronic thrombocytopenia (platelet <50,000 cells/dL)
Stage IV	▪ HIV wasting syndrome, as defined by the CDC ▪ Peumonocytis pneumonia ▪ Recurrent severe bacterial infection pneumonia ▪ Chronic herpes simplex infection (porolabial , genital, or anorectal site for > months or visceral herpes at any site) ▪ Esophageal candidiasis (or candidiasis of trachea , bronichi, orlungs) ▪ Extrapulmonary tuberculosis ▪ Kaposi sarcoma ▪ Cytomegalovirus infection (retinitis or infection of other organs)Central nervous system toxoplasmosis ▪ HIV encephalopathy ▪ Cryptoccosis , extrapulmonary (including meningitis) ▪ Disseminated notuberculosis Mycobacteria infection ▪ Progressive multifocal leukoencephalopthy ▪ Candida of the trachea, bronchi or lungs ▪ Chronic cryptosporidiosis (with diarrhea) ▪ Chronic isosporiasis ▪ Disseminated mycosis (eg histoplasmosis, coccidioidomycosis, penicilliosis ▪ Recurrent notyphoidal salmonella bacteremia ▪ Lymphoma (cerebral or B-cell non-Hodgkin) ▪ Invasive cervical carcinoma ▪ Atypical disseminated leishmaiasis ▪ Symptomatic HIV –associated nephropathy ▪ Symptomatic HIV-associated Cardiomyopathy ▪ Reactivation of American trypansomiasis (menigoencephalitis or mycocarditis).

APPENDIX VI: NATIONAL MANUAL FOR THE MANAGEMENT OF HIV-RELATED OPPORTUNISTIC INFECTIONS AND CONDITIONS [94]

Disease	Management
URTIs	Emergency: Unable to swallow or pharyngeal abscess. *Give IM/IV an_bio_cs and* ***refer.*** Gingivi_s – metronidazole OR co-amoxiclav Pharyngi_s, tracheo-bronchi_s o_en viral, are self-liming & do not require anti _bio_cs. Hard to dis_nguish viral from bacterial pharyngi_s. If fever, LN, exudates treat as bacterial with penicillin although these may occur in viral pharyngi_s. O__s media – (red, bulging ear drum; ± discharge). An_bio_cs – amoxicillin or erythromycin Acute sinusi_s - use saline nasal spray; PLHA o_en need an_biotics (co-amoxiclav, erythromycin or doxycycline) if sinus pain, obstruc_on, purulent discharge, headache, fever & no response to nasal decongestant
Lower Respiratory Tract Infec_ons	An_biotics - high dose amoxicillin or benzyl penicillin - erythromycin if pt penicillin allergic; add erythromycin if pt fails to improve within 3 days or if co-morbidity - very sick – ce_riaxone + macrolide - exacerba_on of COPD – doxycycline OR erythromycin - nosocomial – ce_riaxone OR ci
Gastrointes _nal infec_on	An_bio_cs: not o_en required in HIV -ve pts but indicated in PLHA - ciprofloxacin OR ceftriaxone - plus metronidazole for amoebiasis/protozoa An_helminthics if needed -very sick IV amoxicillin + gentamicin + IV metronidazole. Or IV FQ plus IV metronidazole Consider surgical review. - if Clostridium difficile likely: metronidazole
Community acquired bacteremia Or Sep_caemia	IV amoxicillin + gentamicin OR ce_riaxone alone
Bacterial pneumonia	In patients with no history of antibiotic treatment in the preceding 3 months: high dose amoxicillin at 1g TDS for 10–14 days. Use in all patients including those taking CTX prophylaxis. ☐ In patients with a history of antibiotic use in preceding 3 months use both high dose amoxicillin 1g TDS + erythromycin at 500mg QID for 10-14 days. Other macrolide may be used. ☐ Review patients in 3 days or earlier if worsening. Add macrolide in patients who fail to improve on amoxicillin alone o Alternative first line for outpatients: ☐ Co-amoxiclav alone or with a macrolide ☐ Doxycycline ☐ Cephalosporins such as cefotaxime or ceftriaxone. (Of the 3rd generation cephalosporins, cefuroxime is the least effective against bacterial pneumonia)
Tuberculosis	I 2ERHZ/6HE (4RH*) II 2SRHZE/1RHZE/5RHE III RHZ/6HE (4RH*)
PNEUMOCYSTIS JIROVECI	1st line: Cotrimoxazole (Single strength, SS 400/80; double strength, DS 800/160) given for

PNEUMONIA	21 days Dose: 20mg/kg of the trimethoprim component. (Alternatively, weight divided by 4 gives the number of SS tablets per 24 hr period) **2nd Line**: Clindamycin *plus* Primaquine (dose: Clindamycin 600-900mg 8 hourly *plus* Primaquine 15-30mg/day or Pentamidine Given for 21 days (Dose: Pentamidine 4mg/kg/day IV/IM) **For the severely ill (02 saturation on air < 90%)** Add prednisolone from first day of Treatment (dose: 40mg BD for 5 days, then 40mg daily for 5 days, then 20mg daily for the remaining 11 days)
Candidiasis	Nyastatin mouth drops 500000 units (5 ml) 4x per day for 7-14 days Miconazole gum patch **Systemic therapy if above fails:** Fluconazole 100mmg/day for 7 days Itraconazole 200mg/ day for 7 days (swished in mouth and swallowed on an empty stomach)
HSV-1	Aciclovir 400mg 8 hourly for 7-10 day
Oesophageal Candidiasis	**Preferred:** Fluconazole 200mg stat then 100mg OD PO x 14-21 days. IV if patient cannot swallow **Failure to improve on Fluconazole:** Increase dose to 400-800mg/day OR Itraconazole *solution* 200mg PO x 14-21 days OR Amphotericin B IV 0.3-0.7 mg/kg/day x 14-21 days If no response consider anti-HSV treatment
CMV Oesophagitis	Valganciclovir 900 mg BD x 3 weeks
Herpes Simplex Virus (HSV) Oesophagitis	Aciclovir 800mg 6 hourly x 14-21 days Or Valaciclovir 1g PO TDS x 14-21 days
Aphthous Ulcers	Prednisolone 40mg/day x 7-14 days, then taper
Acute Diarrhoea	Loperamide 4 mg stat then 2 mg after every lose motion (up to 16mg/day) Ciprofloxacin 500mg BD for 5-10 days (or until symptoms improve)±Metronidazole 500mg TDS for 5-10 Erythromycin 500mg QDS X 5days. Or Ciprofloxacin, although resistance occurs
Chronic Diarrhoea	Pt on CXT prophylaxis: Metronidazole + Albendazole. Add Ciprofloxacin if patient febrile Pt mot on CXT prophylaxis: Metronidazole + Albendazole + CTX 960 mg BD x 10 days Entaoebia histolytica (Metronidazole 500mg TDS x 10 days) Gardia lambila (Metronidazole 250 mg TDS x 10 days) cyptosporidia :)ART; nutritional support; anti-diarrhoeal agents)
Herpes Zoster. (dermatology)	Acyclovir 800mg 5 times daily x 7 days OR Valaciclovir 1g TDS for 7 days, started as soon as possible after onset of symptoms or as long as new vesicles arise.
Herpes Simplex Types 1 and 2. (dermatology)	If first ever episode of HSV or severe ulceration, or chronic ulcer give Aciclovir 400mg 5 times daily x 5 days or until no more new lesions. Chronic herpetic ulcers may require longer duration of treatment. 0.5% GV paint and potassium permanganate baths are indicated to keep lesions clean and dry.

	Chronic HSV lesions indicate severe HIV disease thus patient should be prepared for ART. For disturbing and frequent (> 6 episodes per year) recurrences suppressive therapy should be discussed with a senior clinician (given as ACV 400mg BD or Valaciclovir 500mg OD
Toxoplasmosis	**Prefered regimen :** Pyrimethamine 200 mg loading dose, then 50 mg –75 mg/day + Sulfadiazine 1000 mg to 1500mg P.O. 6 hourly + Folinic acid (leucovorin) 10-20mg/day PO Folate is not a substitute for Folinic acid. The dose **Alternative regimen:** Cotrimoxazole: 5mg/kg of Trimethoprim or 25mg/kg of CTX BD per day for 6 weeks (e.g. for 60kg man, 4 SS tablets per day).
CRYPTOCOCCAL MENINGITIS	**Induction:** Amphotericin B (0.7 - 1.0 mg/kg/d) for 2 weeks or until the patient is clinically stable Consolidation phase: Fluconazole 400-800 mg/d for 8 weeks; the higher dose must be used in patients on concomitant rifampicin Maintenance/suppressive phase: Fluconazole 200 mg/d Discontinuation of Fluconazole: Fluconazole can be stopped in patients who have been on ART and have documented immune reconstitution as shown by CD4 consistently above 100 cells/mm3 for at least 6 months. Alternative Treatment Regimen **Induction:** Fluconazole 400-800 mg per day for 2 weeks **Consolidation:** Fluconazole 400-800mg OD for 8 weeks **Maintenance/suppressive** phase: Fluconazole 200 mg/d