Prevalence and Management of Opportunistic Infections in HIV-Infected Children

Mutua Susan Awino
U59/7567/2006

A dissertation submitted in partial fulfilment of the requirements for the award of the degree of Master of Pharmacy in Clinical Pharmacy by the School of Pharmacy of University of Nairobi

September 2008

DECLARATION

This dissertation is my original work and has not been presented anywhere else.

Principal Investigator

Susan Awino Mutua
U59/7567/06
School of Pharmacy
University of Nairobi

Signature ..... Date 17/11/08.....

Supervisor

Dr David Scott Ph.D.
Department Of Pharmaceutics and Pharmacy Practice
School of Pharmacy
University of Nairobi

Signature ..... Date 17/11/08.....

TABLE OF CONTENTS PAGE

ACKNOWLEDGEMENT

I'm especially grateful to Dr David Scott, my research supervisor for his guidance, constructive criticism and encouragement throughout the study.

My sincere thanks also go to all of the following people for their valuable contribution and support towards this dissertation:

Dr. Karimi, for his guidance at various stages of the study.

Mr. Francis Njiri for assisting in data entry and analysis.

Dr. Muiruri, Manager of the Kenyatta National Hospital Comprehensive Care Centre (CCC) and the entire CCC Paediatric Wing team for their hospitality and assistance during data collection.

My colleagues Dr(s) Robert Kamau, Irene Chege, Jackline Ndinda, Johnson Masese, John Nyiligira, Irene Weru and John Mwesigye for their support and warmth of comradeship.

DEDICATION

To my husband, Mr Mutua Mutuku, who constantly challenges me to pursue a life guided by knowledge and inspired by love.

LIST OF ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral (drug)
AZT	Zidovudine
CCC	Comprehensive Care Centre
CMV	Cytomegalovirus
D4T	Stavudine
DDI	Didanosine
DMAC	Disseminated Mycobacterium avium complex
EFV	Efavirenz
ERC	Ethics and Research Committee
HAART	Highly Active Antiretroviral Therapy
KNH	Kenyatta National Hospital
LPV/R	Lopinavir/ritonavir
MOH	Ministry of Health
MMWR	Morbidity and Mortality Weekly Report
NASCOP	National AIDS and STDs Control Programme
OI	Opportunistic Infection
PACTCG	Paediatric AIDS Clinical Trials Group
PCP	*Pneumocystis jirovecii* pneumonia
SDNVP	Single-dose Nevirapine
SPSS	Statistical Package for Social Sciences
STD	Sexually Transmitted Disease
TB	Tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

LIST OF TABLES

FIGURE

ABSTRACT

BACKGROUND: HIV-infected children are more vulnerable to infections due to their immature and immunologically naïve immune system in addition to the immunosuppressive effects of the virus.

OBJECTIVE: To establish the prevalence of targeted primary opportunistic infections (OIs) in HIV-infected children seen at the Kenyatta National Hospital (KNH), Comprehensive Care Centre (CCC), and to evaluate their management.

METHOD: The study was conducted as a hospital-based cross-sectional study. Incidental sampling was used to obtain 196 patient files of HIV-infected children receiving out-patient care at KNH CCC between March 2008 and April 2008. The files were reviewed for occurrence of targeted opportunistic infections in the past 12 months. Medicines prescribed during the study period were assessed for appropriateness and availability at the KNH CCC pharmacy. This information was entered into a data collection form and then analysed using the Statistical Package for Social Sciences (SPSS) software.

RESULTS: Overall, 144 infection episodes occurred among the study participants. The three most common events were bacterial pneumonia (30.1%), tuberculosis (22.4%) and oral candidiasis (12.2%). Prevalence of tuberculosis and bacterial pneumonia correlated significantly with duration on HAART and WHO Stage. A total of 1030 drug-prescriptions were reviewed. Antiretrovirals (44.6%), antibiotics (25.4%) and vitamin supplements (18.5%) were the most prescribed drugs. 112 prescription errors were identified which were: wrong dosage (105), inappropriate choice (4), and contraindicated medicines (3). The majority (86.9%) of prescribed drugs were available at the CCC Pharmacy. Essential medicines that were not available included: anti-tuberculosis drugs, haematinics and anthelmintics.

CONCLUSION: The prevalence of OIs in HIV-infected children varies with pathogen, duration on HAART and WHO Stage. Medicines are generally rationally prescribed to the children. The most common prescription errors were incorrect dosage of cotrimoxazole and antiretrovirals. Most of the medicines prescribed were available at the CCC pharmacy.

RECOMMENDATION: Prescribers and pharmacists should work closely to develop appropriate strategies to address dosing errors particularly of cotrimoxazole and antiretrovirals which are the most commonly prescribed medicines.

1.0 INTRODUCTION

1.1 Background

According to estimates by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO), more than four million children under the age of 15 have been infected with human immuno-deficiency virus (HIV) since the epidemic began [1]. Because HIV infection often progresses quickly to Acquired Immuno-deficiency Syndrome (AIDS) in children, most of the children less than 15 years who have been infected have developed AIDS, and majority of these have died.
In Kenya, about one hundred and fifty thousand children are HIV-infected according to the Kenya Demographic Health Survey [2].

Babies are born with an immature and immunologically naïve immune system, predisposing them to an increased frequency of bacterial infections [3, 4]. The immunosuppressive effects of HIV are additive to those of an immature immune system and place HIV-infected children at particularly high risk of infections. Common childhood infections and conditions are more frequent in HIV-infected children and have a higher case fatality compared to uninfected children. These include diarrhoea, acute lower respiratory tract infections, septicaemia, acute suppurative otitis media, sinusitis and failure to thrive.

Opportunistic infections (OIs) are a major cause of morbidity and mortality in children infected with HIV [3]. The OIs include bacteraemia, bacterial pneumonia, cryptococcal

meningitis, cryptosporidiosis, Cytomegalovirus (CMV) disease, dermatophyte infections, disseminated *Mycobacterium avium* complex (DMAC), Hepatitis B, Hepatitis C, human papillomavirus, herpes simplex virus, herpes zoster, lymphoid interstitial pneumonitis, candidiasis (oesophageal and tracheobronchial disease), *Pneumocystis jirovecii* pneumonia (PCP), systemic fungal infections, toxoplasmosis and tuberculosis.

Successful implementation and maintenance of highly active antiretroviral therapy (HAART), resulting in improved immune status, has been established as the most important factor in control of opportunistic infections among both HIV-infected adults and children [5, 6]. The use of HAART has dramatically changed the incidence, epidemiology and presentation of opportunistic infections among children and adults [7]. As with HIV-infected adults, substantial decreases in mortality and morbidity, including opportunistic infections, have been observed among children receiving HAART [8]. Although the number of opportunistic infections has decreased, the relative prevalence of AIDS-defining infections remains similar to that observed in the pre-HAART era [9].

Treatment of opportunistic infections is an evolving science, and availability of new agents or clinical data on existing agents might change therapeutic options and preferences [1]. As a result, treatment recommendations need to be periodically updated. In comparison with recurrent serious bacterial infections, few of the protozoan, fungal, or viral opportunistic infections complicating HIV are curable with available treatments. For many opportunistic infections, following treatment of the initial infectious episode,

secondary prophylaxis in the form of suppressive therapy is indicated to prevent recurrence of clinical disease.

In order to promote quality of care and cost-effective therapy, it is critical that the medicines used for treatment and prevention of the opportunistic infections are rationally prescribed. Rational use of drugs requires that patients receive medicines appropriate to their clinical needs, in doses that meet their individual requirements, for an adequate period of time, and at the lowest possible cost to them and the community [10].

Inappropriate treatment due to medication errors in children is commonly reported resulting in treatment failure, adverse drug events or even fatalities [11]. Medication errors occur as a result of human mistakes or system flaws which need to be addressed to prevent unnecessary harm. Data related to the efficacy of various therapies for opportunistic infections in adults can generally be extrapolated to children, but issues related to drug pharmacokinetics, formulation, ease of administration, drug dosing and toxicity require special considerations among children [1]. Young children in particular metabolize drugs differently from adults and older children. However, data on appropriate drug dosing recommendations for children aged <2 years often are lacking.

Access to much needed treatment and care in Africa is often hindered by poverty which is widespread [12]. The capacity of individuals and households to cope with HIV and AIDS has been known to depend on their initial endowment of assets - both human and financial. Even the non-poor find their resources diminished by their experience of

infection (morbidity and death), and there is increasing evidence in urban communities of an emerging class of those recently impoverished by the epidemic. Thus, it is crucial that the HIV care services especially medicines (both antiretrovirals and medicines for opportunistic infections) are made accessible in terms of availability, affordability, geographic accessibility and acceptability.

1.2 Problem Statement

More than 1500 children become infected with HIV every day according to UNAIDS. Since the beginning of the pandemic, of the over 5 million infants who have been infected with HIV, 90% are reported to have been born in Sub-Saharan Africa. HIV infection is a major contributing factor to childhood disease and mortality in developing countries, and it is threatening gains made in infant and child survival and health over recent decades. Several reasons have been cited for the higher mortality of HIV-infected African children as compared to their counterparts in developed countries which include intercurrent infections, malnutrition and limited access to care and treatment.

HIV-infected children have increased susceptibility to infections and although they suffer from the same common childhood illnesses as those who are not infected, the illnesses are more frequent, last longer and may respond poorly to usual treatments. In advanced HIV infection, opportunistic infections occur. There are few comprehensive studies documenting the etiological cause of infections and death in HIV-infected children in Africa. It is therefore difficult to obtain a comprehensive picture of the common

conditions over the course of HIV infection for purposes of focussing prevention and treatment strategies of highly prevalent infections.

In addition, easily treatable conditions continue to cause deaths in HIV-infected children in Africa. This has mainly been attributed to inability to access preventive and treatment services in terms of *availability*, *affordability*, *geographic accessibility* and *acceptability*.. Access to care and treatment remains elusive for the majority of persons in Africa, mostly due to socio-economic constraints. Poverty, which is widespread in Africa, has played a negative role in efforts aimed at containing the HIV scourge. Poor living conditions (crowded, unhygienic environment) and malnutrition expose the HIV-infected child to infections and often, prescribed medications are not affordable to caregivers.

Whereas the KNH CCC Pharmacy provides antiretroviral drugs (ARVs) and selected medicines free-of-charge to the paediatric patients, prescribed medicines are not always available. Bearing in mind that KNH is a public hospital with most patients being of low socio-economic class, the majority are unable to afford missing medicines and often return having deteriorated.

The incidence of medication errors and the risk of serious errors occurring in children are usually significantly greater than in adults. At KNH CCC, the HIV-infected children are seen by various cadres of staff including junior clinicians (i.e. medical students, clinical officers and interns) most of whom work on a rotational basis. There is therefore a high probability of irrational drug use as a result of prescribing errors and/or inappropriate

therapy being given in terms of choice of drug, dosage, duration of therapy and interactions.

It is against this background that this study sought to identify the common opportunistic infections among children seen at the KNH CCC, evaluate their management and accessibility of prescribed medicines.

1.3 Study Justification

Since most of the opportunistic infections known to affect HIV-infected children are readily treatable and/or preventable, with most of the treatments being simple, available and affordable, every effort should be made to facilitate proper management.

There is need to establish local prevalence of these infections and evaluate appropriateness and accessibility of therapy given for their management. The findings would provide a viable platform for informed and useful policy and operational decisions towards improving and strengthening care of HIV-infected children.

Knowledge of the prevalence of infections will guide prioritisation of resources towards the more common infections and evidence of inappropriate management will support development of suitable intervention strategies to promote rational selection, procurement and use of medicines.

1.4 Goal of Study

To improve the management of opportunistic infections in HIV-infected children at the Kenyatta National Hospital (KNH), Comprehensive Care Centre (CCC).

1.5 Objectives

1.5.1 General

To establish the prevalence of opportunistic infections in HIV-infected children at the KNH CCC and to evaluate their management.

1.5.2 Specific

1. To establish the prevalence of targeted primary opportunistic infections in HIV-infected children at the KNH CCC.
2. To determine whether medicines are rationally prescribed in management of these infections.
3. To assess availability and accessibility of the medicines at the CCC Pharmacy.

1.6 Research Questions

1. Which are the commonest opportunistic infections among HIV-infected children at KNH CCC?
2. Are the medicines used for the management of the opportunistic infections rationally prescribed?
3. Are prescribed medicines accessible to the patients?

2.0 LITERATURE REVIEW

2.1 Introduction

At the end of 2007, 2.1 million [1.9 million to 2.4 million] children younger than 15 years were estimated to be living with HIV and 420 000 [350 000–540 000] were newly infected [13]. Globally, 290 000 [270 000–320 000] children younger than 15 years died of HIV-related causes in 2007. About 90% of the children living with HIV are in sub-Saharan Africa. HIV is adversely affecting the overall health of children, especially in countries with a high HIV burden. HIV has been the leading cause of death among children younger than five years of age in a number of African countries [14]. Mother-to-child HIV transmission has been found to account for about 95% of HIV acquisition in children.

In 2006, at the second United Nations General Assembly High Level Meeting on HIV/AIDS, countries agreed to work towards the goal of "universal access to comprehensive prevention programmes, treatment, care and support" by 2010 [15]. These global commitments complement the health-related United Nations Millennium Development Goals, which have established targets to reduce child mortality, improve maternal health and combat HIV/AIDS, malaria and other major diseases by 2015 [16].

While significant advances have been made in the implementation of programming for preventing the mother-to-child transmission of HIV in low- and middle-income countries,

and in scaling up antiretroviral care and treatment for children in the past few years, little seems to be happening with regard to combating many of the HIV associated infections.

In HIV-infected children, the immunosuppressive effects of HIV are additive to those of an immature immune system and place HIV-infected children at particularly high risk of opportunistic infections [3]. Very early in HIV infection, the ability to respond to pathogens and other antigens, and the ability of the immune system to recall the memory of past exposure is diminished. In addition, HIV causes a decline in neutrophils. Prevalence of opportunistic infections increases with HIV disease progression, often occult and non-localizing, caused by unusual organisms and with unusual presentation.

An important mode of acquisition of opportunistic infections among children is from an infected mother to her child [1]. HIV-infected women co-infected with opportunistic pathogens might be more likely to transmit these infections to their infants than women without HIV infection. For example, greater rates of perinatal transmission of hepatitis C and cytomegalovirus have been reported from HIV-infected than uninfected women [17, 18].

In addition, HIV-infected women or HIV-infected family members co-infected with certain opportunistic pathogens might be more likely to transmit these infections horizontally to their children, resulting in an increased likelihood of primary acquisition of such infections in the young child. For example, *Mycobacterium tuberculosis* infection among children primarily reflects acquisition from family members with active

tuberculosis (TB) disease, and increase in the incidence and prevalence of tuberculosis among HIV-infected persons is well documented [19]. HIV-exposed or –infected children have a higher risk for exposure to *M. tuberculosis* than comparably aged children in the general population because of residence in households with HIV-infected adults.

Various factors have been associated with increased risk for opportunistic illnesses in HIV-infected children including low CD4+ T-lymphocyte percentages and malnutrition [3]. Opportunistic illnesses occurring in the paediatric HIV-infected population in the HAART era are mainly in children with persistently low CD4+ T-lymphocyte percentages.

Ylitalo *et al.*, [20] found that older age (age >10 years) at HAART initiation was associated with increased risk of a first OI compared with initiating HAART in children younger than 2 years. Lack of a sustained response to HAART rather than age at or duration of HAART use was found to be predictive of OI risk.

In the African context, widespread malnutrition has been found to compound the problem of opportunistic infections in children. HIV infection increases nutrient requirements, and at the same time impairs nutrient intake and uptake, while poor nutrition increases susceptibility to opportunistic infections [21].

Babirekere-Iriso E. *et al* [22] in a study of bacteraemia in severely malnourished children in an HIV-endemic setting, found that forty-four per cent of the severely malnourished children studied were HIV-infected and that HIV infection predisposed children with malnutrition to recurrent bacterial infections and a high risk of bacteraemia.

The effects of malnutrition on the immune system are well known and include decreases in CD4 T-cells, suppression of delayed hypersensitivity, and abnormal B-cell responses [23, 24]. In Africa, malnutrition and food insecurity are endemic and nearly 40% of African children < 5 years old are stunted due to chronic nutritional deprivation [12]. The immune suppression caused by protein-energy malnutrition is similar in many ways to the effects of HIV infection [25, 26] and various studies have demonstrated that weight loss and wasting were associated with increased risk of opportunistic infection and shorter survival time in HIV-positive adults, independent of their immune status [27, 28, 29].

CD4% was found to correlate significantly with increasing grades of protein energy malnutrition ($P < 0.05$) [30]. Malnutrition and HIV/ AIDS are thus synergistic in creating a vicious cycle that additively weakens the immune system increasing susceptibility to infections.

2.2 Opportunistic Infections

Clinical manifestations of HIV in children have been found to be different from those in adults with the main presentations being tuberculosis and failure to thrive [31]. In the study, of the 55 children enrolled, 25 (67.5%) had tuberculosis and 18 (48.6%) had failure to thrive. Non-specific features such as recurrent bacterial infection, oral candidiasis and chronic diarrhoea were other manifestations.

Agarwal D. *et al.,* [30] found that fever (53%), chronic diarrhoea (36%), and cough (29%) were the commonest presenting symptoms with the most common opportunistic infection being tuberculosis.

A retrospective review of the profile of HIV infected children attending an HIV clinic in South India found the following to be the common clinical manifestations in the children at presentation: oral candidiasis (43%), pulmonary tuberculosis (35%), recurrent respiratory infections (26%), bacterial skin infection (21%), papulo-pruritic dermatitis (19%), hepatosplenomegally and lymphadenopathy (14%) each and chronic diarrhoea (7%) [32].

Contemporary clinical care seems to have altered the natural history of opportunistic disease [33]. This was demonstrated in a study conducted in an urban population (USA) infected with HIV. It was found that in the patients studied, the incidences of secondary P. carinii pneumonia, cryptococcal meningitis, and herpes zoster have declined in the past 5 years as a result of effective preventive strategies. The incidences of primary P. carinii

pneumonia and Kaposi sarcoma appeared to be declining compared with historical estimates and these and other OIs were first occurring at more advanced immunosuppression than in the past. Continued efforts are needed to monitor and develop effective strategies for managing opportunistic diseases.

The frequency of different opportunistic pathogens was shown to vary among HIV-infected children in the pre-HAART era by age, pathogen, previous opportunistic infection, and immunologic status [34]. In the pre-HAART era, the most common opportunistic infections among children in the United States were serious bacterial infections (with pneumonia, often presumptively diagnosed, and bacteremia being most common), herpes zoster, disseminated Mycobacterium avium complex (DMAC), Pneumocystis jiroveci (formerly carinii) pneumonia (PCP), and candidiasis (esophageal and tracheobronchial disease). Less commonly observed opportunistic infections included cytomegalovirus disease, cryptosporidiosis, tuberculosis, systemic fungal infections, and toxoplasmosis. History of a previous AIDS-defining opportunistic infection was a predictor of developing a new infection. Although the majority of infections occurred among children who were substantially immunocompromised, serious bacterial infections, herpes zoster, and TB occurred across the spectrum of immune status.

Gona *et al.*, [35] demonstrated in a prospective cohort study that the four most common infections were bacterial pneumonia, herpes zoster, dermatophyte infections, and oral candidiasis. Bacteremia, Pneumocystis jirovecii pneumonia, disseminated

Mycobacterium avium complex, lymphoid interstitial pneumonitis, systemic fungal infection, cytomegalovirus retinitis, and tuberculosis were less common.

Introduction of HAART has decreased mortality and progression to AIDS in perinatally HIV-1-infected children [5]. Progressive reductions of both mortality and rates of class B and C clinical events, including organ complications, have been evidenced in the HAART era.

The Swiss HIV Cohort study showed that the risk of developing an OI for a person receiving potent antiretroviral therapy is highest during the initial months of therapy [36].

The importance of HAART can not be over emphasized in management of HIV-infected persons. HAART has resulted in a decrease in hospitalization and mortality rates among HIV-infected children [37]. It has also led to an increase in the number of persons living with HIV. OIs are still occurring, especially when patients access care late during the course of disease. Even after accessing care, persons may develop OIs because of lack of prescription for prophylaxis, antiretroviral drug resistance, or poor adherence to therapy.

In USA, CDC has developed population-based approaches for surveillance of HIV disease progression, OIs, and therapies with the goal of making these data available in more geographic areas to help assess public health and health-care programs [38].

Most of the clinical guidelines for the prevention and management of opportunistic infections in HIV-infected individuals have been developed on the basis of natural history data collected in the USA. However, geographical differences have been shown to exist in the prevalence of HIV-related opportunistic infections [39]. Hence local data should be used to define local priorities for prophylaxis and treatment of opportunistic infections.

2.3 Rational Prescribing for Opportunistic Infections in Children

The rational use of drugs requires that patients receive medicines appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and the community [10]. Principles of rational therapeutics emphasize the importance of prescribing medicines such that the right patient receives the right drug at the right dose and at an affordable cost. Rational drug use can only be achieved by practice of accurate diagnosis, rational prescribing and correct dispensing accompanied by proper patient use.

Various guidelines have been developed to assist health workers make accurate diagnoses and prescribe rationally in managing of opportunistic infections in children [3, 40, 41, 42]. However, rational prescribing among children is challenged by requirements such as determination of dosage (by age, weight, height and/or surface area) and limited availability of suitable preparations. Medication errors are now recognized as an important cause of adverse drug events in paediatric practice [43]. These errors include inappropriate choice, incorrect dosing, over-prescribing, under-prescribing and issuing of

contraindicated medicines. Medication errors can produce a variety of problems ranging from minor discomfort to death.

The paediatric population encompasses a very heterogeneous group, from the smallest premature infant to fully-grown adolescents. As a result, doses of the same drug within one institution's paediatric patient population may vary by more than ten-fold [44]. When dosages must be calculated by patient weight, and very small amounts of drug are needed, there is considerable risk for mathematical errors [45]. Several studies have documented the risk for mathematical errors by prescribers [46, 47, 48, 49, 50].

Lesar TS [49] in a retrospective review of medication orders found that a significantly greater number of errors involved paediatric patients than adults. Of those errors made in children, 56.1% would have resulted in an overdose if not detected. The most frequent type of serious error was decimal point misplacement, occurring in 27.9% of the paediatric errors reported. Failing to divide the total daily dose into individual doses occurred in 16.3% of the cases.

Rowe *et al.*, [50] examined the same problem, but through different means to evaluate the ability of medical residents to determine the appropriateness of drug dosages for children. The authors compared results from 1993 (34 residents) and 1995 (30 residents). They found a significant decrease ($p = 0.03$) in medication errors with a significant decrease in the total number of wrong calculations ($p = 0.01$). The authors speculate that these improvements may have been the result of a concerted effort to train residents in dosage

calculations. Serious errors, however, showed no decline and ten-fold dosing calculation error were identified despite the use of calculators. The examinees also frequently failed to recognize doses deliberately set to be excessive for the test patient.

Computer calculated doses have been found to significantly reduce mathematical errors [51], but other risk factors have to be concurrently addressed to achieve maximum benefit.

In another study, Lesar *et al.,* [52] found that the most common groups of factors associated with errors were those related to knowledge and the application of knowledge regarding drug therapy; knowledge and use of knowledge regarding patient factors that affect drug therapy; use of calculations, decimal points, or unit and rate expression factors; and nomenclature factors (incorrect drug name, dosage form, or abbreviation). This led to the conclusion that since several easily identified factors are associated with a large proportion of medication prescribing errors, by improving the focus of organizational, technological, and risk management educational and training efforts using the factors commonly associated with prescribing errors, risk to patients from adverse drug events should be reduced.

Kunac *et* al., [53] demonstrated that over half of medication-related events that cause patient harm are preventable. In a study conducted among hospitalised children in New Zealand, he found that the most commonly implicated in the harmful or potentially harmful preventable events, and hence the best targets for prevention were: dosing errors,

particularly during the prescribing stage of the medication use process, and use of antibacterial agents, particularly when administered by the intravenous route.

Errors identified in a study of prescribing practices of doctors attending to under fives in a children's outpatient clinic in Nigeria led to recommendation for developing and circulating easy to use treatment guidelines for diseases commonly seen in the centre, a regular audit of the application of these guidelines and institution of continuing medical education of doctors on rational drug use and evidence based medicine [54].

Causes of medication errors are usually multifactorial and it is recommended that when investigating medication errors, particular focus should be placed on system changes such as educating health care providers, use of technologic advances to reduce errors, such as computerized prescriber order-entry and automated dispensing devices, implementation of policies to enforce appropriate prescribing and accurate drug preparation and administration, and development of multidisciplinary continuing quality improvement programs to oversee pediatric drug administration [43, 44].

2.4 Access to Medicines

Every year infectious diseases are said to kill about 13 million people (about 30.000 deaths a day) with almost half of the victims being children younger than 5 years old, most of them belonging to developing countries [55]. Most of the premature deaths and the incapacity cases associated to infectious diseases could be avoided if the poor had access to medicines.

According to World Health Organization (WHO), in the developing countries about 2,000 million people lack access to essential medicines [56]. This has led to international campaign for the access to essential medicines by some non-governmental organizations like Act Up, Treatment Action Campaign, Doctors Without Borders and Intermon Oxfam.

Many of the drugs needed to treat the opportunistic infections present during advanced HIV infection and AIDS are prohibitively expensive for both developing countries and most individuals in those countries [57]. The imposition of World Bank and International Monetary Fund structural adjustment programs together with decreased household purchasing power during the 1990s has led to increased demand for public sector services amid reduced public expenditure. The private sector is increasingly taking over the drug supply in developing countries, driving the cost of drugs out of the range of affordability for the vast majority of the poor.

One of the strategies suggested to contain the cost of drugs has been for governments to develop and implement an integrated national drug policy based upon the concept of essential drugs and their rational use [56]. The World Health Organization advocates for governments to adopt the Essential Drugs and Medicines Policy (EDM) which aims 'to help save lives and improve health by closing the huge gap between the potential that essential drugs have to offer, and the reality that for millions of people-particularly the poor and disadvantaged- medicines are unavailable, unaffordable, and unsafely used'.

Essential medicines are regarded as those that satisfy the priority health care needs of the population [56]. They are selected with due regard to public health relevance, evidence on efficacy and safety and comparative cost effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford.

The concept of essential medicines is that a limited number of carefully selected medicines based on agreed clinical guidelines leads to a more rational prescribing, to better supply of drugs and lower costs [57].The practical implication of the essential medicines concept is that national essential medicines lists and national drug formularies, together with clinical guidelines, should serve as a basis of formal education and in-service training of health professionals, and of public education about drug use. They should also serve as the main basis for public sector drug procurement and distribution, as well as for drug donations.

The debate on access to essential medicines, which was live in the late 1970s and 1980s when strong pressure from public health advocates led the pharmaceutical industry to accept the concept, is now back on the international health policy agenda [58]. Currently, the Essential Drugs List (EDL) forms an integral part of national drug policies in several countries, including Kenya, guiding the selection of drugs on the basis of public health relevance, efficacy, safety and cost.

The WHO medicines strategy provides a framework for coordinated action in essential drugs and medicines by WHO and its strategic partners to addresses four major objectives [56]:

a) Policy - Ensure commitment of all stakeholders to national drug policies, to coordinated implementation, and to monitoring of policy impact;
b) Access - Ensure equitable availability and affordability of essential drugs, with an emphasis on diseases of priority;
c) Quality and safety - Ensure the quality, safety and efficacy of all medicines by strengthening and putting in to practice regulatory and quality assurance standards and
d) Rational use - Ensure therapeutically sound and cost effective use of drugs by health professionals and consumers.

3.0 DESIGN AND METHODOLOGY

3.1 Study Area

Kenyatta National Hospital (KNH), Comprehensive Care Centre (CCC).

KNH is the largest public teaching and referral hospital in East Africa. The KNH CCC is an out-patient clinic that serves as both a primary care centre and a public referral centre for HIV/AIDS patients from all over Kenya. Currently the Centre has over 5000 HIV-infected patients enrolled of whom approximately 700 are children.

3.2 Study Population

Children infected with HIV/AIDS seen at the CCC during the course of the study.

3.2.1 Inclusion Criteria

a) Files of HIV-infected children seen at the KNH CCC between March 2008 and April 2008. Children defined as persons aged less than 18 years.

b) Complete files.

3.2.2 Exclusion Criteria

a) File (patient) previously included/counted.

b) Files of HIV-exposed children with no confirmatory HIV positive results.

c) Incomplete patient files with missing pages resulting in loss of information.

3.3 Study Design

The study was a hospital-based cross-sectional study conducted over 2 months between March 2008 and April 2008.

3.4 Sampling Size/Procedure

From anecdotal information, the point prevalence of infections in HIV-infected children seen at KNH CCC was estimated to be between 10% to 20% *(information obtained from clinicians in the KNH CCC).* Using this range, the estimated average prevalence was assumed to be 15%.

Thus, the sample size for the study was calculated on the basis of a prevalence of 15%, at 5% precision and a 95% level of confidence.

The Fischer *et al* formula for determining sample size was used;

$$n = \frac{Z^2pq}{d^2}$$

Where;

n = Sample size

Z = 1.96 Standard normal deviate at required confidence level

p = 0.15 Estimated prevalence or proportion

q = 1 – p = 0.85

d = 0.05 Precision

$$n = \frac{1.96^2 \times 0.15 \times 0.85}{0.05^2} = \textbf{196 patients}$$

Incidental sampling was used to obtain the 196 patient files. All files of children meeting the inclusion criteria seen each day at the clinic during the study period were collected for extraction of required information.

3.5 Data Collection Method

Files of patients seen daily on weekdays from 10th March 2008 to 28th April 2008 were obtained by simple random sampling. Files of children who were seen by different clinicians in different rooms were randomly picked and reviewed within the KNH CCC. The data extracted from the files were entered into a pre-designed data collection form (Appendix 1).

3.6 Data Analysis Procedure

The data collected were transferred into a Microsoft Access database and then analyzed using SPSS software version 13.0.

The level of significance was set at 0.05 and p-values less than or equal to 0.05 were considered statistically significant.

3.7 Data Quality Control

The data collection form was piloted before use by randomly sampling 50 patient files of HIV-infected children seen at the KNH CCC. The tool was then adjusted and reformatted to facilitate effective and efficient data collection.

The data entered by the statistician into the Microsoft Access database was routinely checked for accuracy and completeness. Errors and omissions identified were rectified. On completion of data entry, data cleaning was done to correct any mistakes that might have occurred during data entry.

3.8 Ethical Considerations

Approval to carry out the study

Permission to carry out the study was obtained from the Ethics & Research Committee at Kenyatta National Hospital (Appendix 2).

Confidentiality

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

Benefits from the study

- Matters of concern in patient management were communicated in line with standard professional practice.
- The findings will be communicated to the primary care givers to contribute in improving the quality of care of the HIV-infected children at the KNH CCC.

Risks involved: There were no risks to the patients involved in the study.

Voluntariness and Informed consent: These were not applicable, as only patient files were used for the study.

4.0 RESULTS

4.1 Demographic Characteristics

A total of one hundred and ninety six patient files were reviewed and the characteristics of the patients are shown below.

4.1.1 Gender Distribution

The population studied had an even distribution of gender with the male being slightly more than the female (Table 1).

Table 1: Gender Distribution

Gender	Number	Percentage
Male	102	52.0%
Female	94	48.0%
Total	**196**	**100.0%**

4.1.2 Age Distribution

The overall mean age was 6.7 years with the minimum and maximum ages being 0.5 years and 17.9 years respectively (Table 2). The female patients were slightly older with a mean age of 7.5 years compared to the males' mean of 5.9 years.

Table 2: Age Distribution

Age (in years)	Mean	Range
Male	5.9	0.7 – 16.0
Female	7.5	0.5 – 17.9
Overall	6.7	0.5 – 17.9

4.1.3 Grouped Age Distribution

The commonest age group was 5 years or below which constituted 45.4% of the patients (Table 3). Children aged 15 years or above were the fewest (3.6%).

Table 3: Grouped Age Distribution

Age Group	Number	Percentage
Upto 5 years	89	45.4%
Above 5 years to 10 years	65	33.2%
Above 10 years to 15 years	35	17.9%
Above 15 years	7	3.6%
Total	**196**	**100.0%**

4.1.4 WHO Stage Distribution

The commonest WHO stage was Stage 3 which constituted 48.0% of the patients studied followed by Stage 2, then Stage 4 and lastly Stage 1 (Table 4).

Table 4: WHO Stage Distribution

Current WHO stage	Number	Percentage
Stage 1	3	1.5%
Stage 2	59	30.1%
Stage 3	94	48.0%
Stage 4	40	20.4%
Total	**196**	**100.0%**

4.1.5 Relationship Between WHO Stage and Age

Generally, children in Stage 1 were slightly older (mean age 8.31 years) while those in stage 4 were slightly younger (mean age 6.14 years) (Table 5).

The minimum and maximum ages were somewhat similar across the WHO Stages.

Table 5: Relationship between WHO Stage and Age

Current WHO stage	Mean Age	Range
Stage 1	8.31	2 – 17
Stage 2	7.04	1 – 18
Stage 3	6.66	0 – 16
Stage 4	6.14	1 – 16
Overall	6.69	0 – 18

4.1.6 Antiretroviral Therapy Initiation

The majority (78.6%) of the children had been initiated on antiretroviral therapy (Table 6).

Table 6: Antiretroviral Therapy Initiation

Antiretroviral Therapy	Number	Percentage
Children on Antiretroviral Therapy	154	78.6%
Children NOT on Antiretroviral Therapy	42	21.4%
Total	**196**	**100.0%**

4.1.7 Duration of Antiretroviral Therapy

Most (56.5%) of the children on antiretroviral therapy had been on treatment for less than 1 year (Table 7).

Table 7: Duration of Antiretroviral Therapy

Duration of Antiretroviral Therapy	Number	Percentage
Up to 1 year	87	56.5%
Above 1 year to 2 years	37	24.0%
Above 2 years to 3 years	22	14.3%
Above 3 years	8	5.2%
Total	**154**	**100.0%**

Age correlated significantly with duration on HAART (p = 0.004) (Table 8). The youngest age group (Upto 5 years) had been on HAART for the shortest period (mean = 11.0 months) while the older ones (Above 15 years) had been on HAART for the longest period (mean = 30.2 months).

Table 8: Interaction Between Age and Duration of Antiretroviral Therapy

	Duration on HAART in months	
Age groups	**Mean**	**P value**
Upto 5 years	11.0	0.004
Above 5 years to 10 years	16.4	
Above 10 years to 15 years	12.7	
Above 15 years	30.2	

4.2 Prevalence of infections

In this study the Chi square test of significance was applied in comparing the prevalence of the targeted infections among age groups, between gender, between those on HAART and those not on HAART, among those on different durations of HAART and WHO stages. Statistical significance was only considered where $p < 0.05$.

4.2.1 Current Opportunistic Infections

The majority of the children (85.7%) who came to the CCC did not have any opportunistic infection at the time of the study (Table 9). However, 28 (14.3%) had an opportunistic infection with 24 having one opportunistic infection each and 4 having two opportunistic infections each.

Table 9: Current Opportunistic Infections

Number of Infections	Number of Patients	Percentage
0	168	85.7%
1	24	12.2%
2	4	2.0%
Total	**196**	**99.9%**

Among the children who presented with opportunistic infections at the time of the study, the commonest opportunistic infection was tuberculosis (7.1%) followed by bacterial pneumonia (5.1%) (Table 10).

Table 10: Prevalence of Current Opportunistic Infections

Opportunistic Infection	Number	% (n=196)
Bacterial Pneumonia	10	5.1%
Cryptococcal Meningitis	2	1.0%
Herpes Simplex	0	0.0%
Kaposi's Sarcoma	1	0.5%
Lymphoid Pneumonia	0	0.0%
Oesophageal Candidiasis	1	0.5%
Oral Candidiasis	3	1.5%
Pneumocystis Pneumonia	0	0.0%
Tuberculosis	14	7.1%
Varicella Zoster	1	0.5%
Total Infection Episodes	**32**	

4.2.2 Opportunistic Infections in the past 12 months

Twenty eight (14.3%) patients had not suffered any opportunistic infection in the past 12 months (Table 11). The remaining 168 (85.7%) patients had suffered at least one episode of infection.

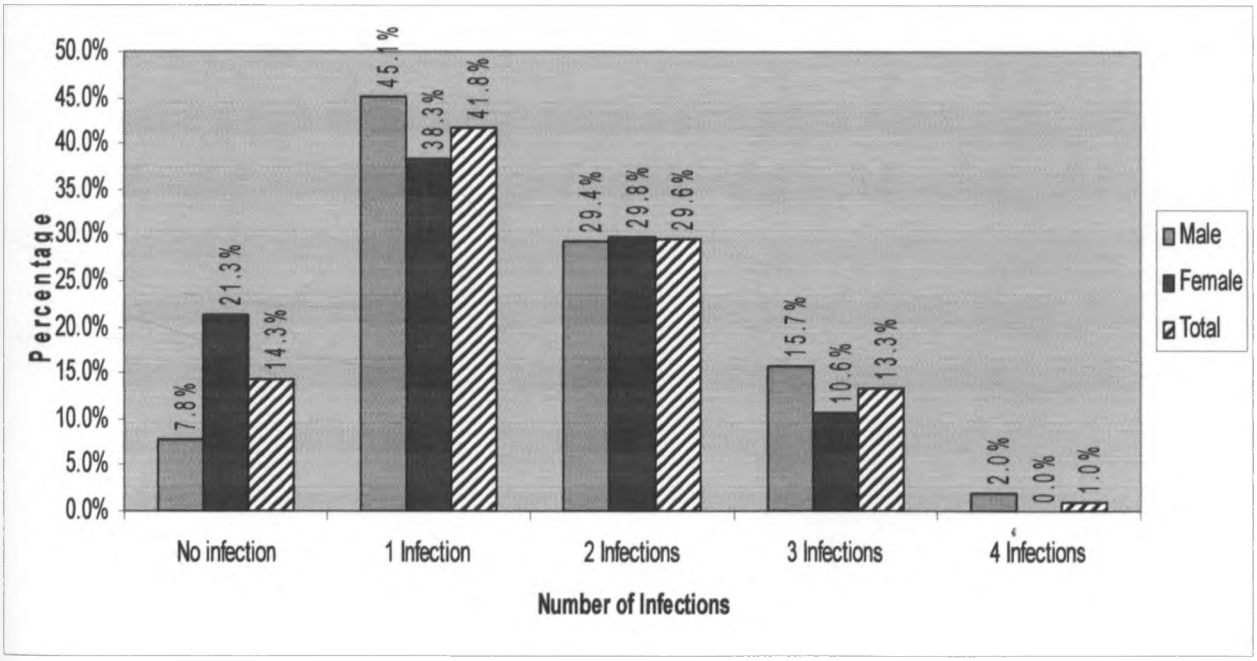
Table 11: Opportunistic Infections in the Past 12 months

Number of Infections	Number of Patients	Percentage
0	28	14.3%
1	82	41.8%
2	58	29.6%
3	26	13.3%
4	2	1.0%
Total	**196**	**100%**

4.2.3 Number of Infections per Patient

Overall and for both genders, the most common number of infections per patient was one (Figure 1). 45.1% of males, 38.3% of females and 41.8% of all the children had suffered from one infection.

Figure 1: Number of Infections per patient



4.2.4 Overall Prevalence of Opportunistic Infections

Overall, a total of 144 infection episodes occurred among the study participants (Table 12). The commonest opportunistic infection was bacterial pneumonia occurring in 59 (30.1%) patients followed by tuberculosis (22.4%) and oral candidiasis (12.2%).

Table 12: Overall Prevalence of Opportunistic Infections

Opportunistic Infection	Number	% (n=196)
Bacterial Pneumonia	59	30.1%
Cryptococcal Meningitis	3	1.5%
Herpes Simplex	1	0.5%
Kaposi's Sarcoma	2	1.0%
Lymphoid Pneumonia	1	0.5%
Oesophageal Candidiasis	4	2.0%
Oral Candidiasis	24	12.2%
Pneumocystis Pneumonia	3	1.5%
Tuberculosis	44	22.4%
Varicella Zoster	3	1.5%
Total Infection Episodes	**144**	

4.2.5 Opportunistic Infection Prevalence among Age groups

Occurrence of opportunistic infections correlated significantly with age group ($p < 0.001$) (Table 13). More children aged 10 years or below (90.9%) had suffered at least one infection compared to those above 10 years (66.7%). However the older children were much fewer.

Table 13: Occurrence of Opportunistic Infections between age groups

Age	At least one infection	No Infection	p value
Upto 10 years (n=154)	140 (90.9%)	14 (9.1%)	<0.001
Above 10 years (n=42)	28 (66.7%)	14 (33.3%)	
Total (n=196)	**168 (85.7%)**	**28 (14.3%)**	

Age group did not have significant association with prevalence of individual opportunistic infections (Table 14). For all the opportunistic infections the p value was greater than 0.05.

Table 14: Comparison of Prevalence of Individual Opportunistic Infection among Age Groups

	Upto 5 years (n=89)		Above 5 years to 10 years (n=65)		Above 10 years to 15 years (n=35)		Above 15 years (n=7)		P values
Opportunistic Infection	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	
Bacterial Pneumonia	30	33.7%	22	33.8%	7	20.0%	0	0.0%	0.127
Cryptococcal Meningitis	2	2.2%	1	1.5%	0	0.0%	0	0.0%	0.812
Herpes Simplex	1	1.1%	0	0.0%	0	0.0%	0	0.0%	0.751
Kaposi's Sarcoma	1	1.1%	0	0.0%	1	2.9%	0	0.0%	0.589
Lymphoid Pneumonia	0	0.0%	1	1.5%	0	0.0%	0	0.0%	0.567
Oesophageal Candidiasis	1	1.1%	1	1.5%	2	5.7%	0	0.0%	0.397
Oral Candidiasis	13	14.6%	5	7.7%	4	11.4%	2	28.6%	0.324
Pneumocystis Pneumonia	2	2.2%	1	1.5%	0	0.0%	0	0.0%	0.812
Tuberculosis	24	27.0%	12	18.5%	6	17.1%	2	28.6%	0.502
Varicella Zoster	0	0.0%	3	4.6%	0	0.0%	0	0.0%	0.105
Total Infection Episodes	**74**		**46**		**20**		**4**		0.401

4.2.6 Comparison of Infection Prevalence between Genders

No significant association was found between occurrence of opportunistic infections and gender ($p = 0.070$) (Table 15).

Table 15: Occurrence of Opportunistic Infections between Genders

Gender	At least one infection	No Infections	P value
Female (n=94)	74 (78.7%)	20 (21.3%)	0.070
Male (n=102)	94 (92.2%)	8 (7.8%)	
Total (n=196)	**168 (85.7%)**	**28 (14.3%)**	

Also there was no statistical significance in the variation of prevalence of individual infections between males and females (Table 16). For all the opportunistic infections the p value was greater than 0.05.

Table 16: Comparison of Prevalence of Individual Opportunistic Infection between Genders

	Female (n=94)		Male (n=102)		
Opportunistic Infection	**No.**	**%**	**No.**	**%**	**P values**
Bacterial Pneumonia	26	27.7%	33	32.4%	0.474
Cryptococcal Meningitis	1	1.1%	2	2.0%	0.609
Herpes Simplex	0	0.0%	1	1.0%	0.336
Kaposi's Sarcoma	1	1.1%	1	1.0%	0.954
Lymphoid Pneumonia	1	1.1%	0	0.0%	0.296
Oesophageal Candidiasis	1	1.1%	3	2.9%	0.353
Oral Candidiasis	8	8.5%	16	15.7%	0.126
Pneumocystis Pneumonia	1	1.1%	2	2.0%	0.609
Tuberculosis	18	19.1%	26	25.5%	0.288
Varicella Zoster	3	3.2%	0	0.0%	0.069
Total Infection Episodes	**60**		**84**		0.116

4.2.7 Comparison of Infection Prevalence by WHO Stage

There was a significant statistical correlation between occurrence of opportunistic infections and WHO stage ($p<0.001$) (Table 17).The percentage of persons who had suffered at least one opportunistic infection increased with 'increasing' WHO stage.

Table 17: Occurrence of Opportunistic Infections among WHO Stages

Current WHO Staging	At least one infection	No Infections	p value
Stage 1 (n=3)	0 (0%)	3 (100%)	<0.001
Stage 2 (n=59)	47 (79.7%)	12 (20.3%)	
Stage 3 (n=94)	84 (89.4%)	10 (10.6%)	
Stage 4 (n=40)	37 (92.5%)	3 (7.5%)	
Total (n=196)	**168 (85.7%)**	**28 (14.3%)**	

WHO stage correlated significantly with the prevalence of bacterial pneumonia ($p = 0.012$) and tuberculosis ($p = <0.001$) (Table 18). The prevalence of both infections increased with deteriorating WHO stage. The overall number of infection episodes also had a significant statistical correlation with the WHO Stages ($p = 0.0001$).

Table 18: Comparison of Prevalence of Individual Opportunistic Infection by WHO Stage

	Stage 1 (n=3)		Stage 2 (n=59)		Stage 3 (n=94)		Stage 4 (n=40)		
Opportunistic Infection	No.	%	No.	%	No.	%	No.	%	P values
Bacterial Pneumonia	0	0.0%	9	15.3%	34	36.2%	16	40.0%	0.012
Cryptococcal Meningitis	0	0.0%	0	0.0%	2	2.1%	1	2.5%	0.697
Herpes Simplex	0	0.0%	1	1.7%	0	0.0%	0	0.0%	0.506
Kaposi's Sarcoma	0	0.0%	0	0.0%	0	0.0%	2	5.0%	0.049
Lymphoid Pneumonia	0	0.0%	0	0.0%	1	1.1%	0	0.0%	0.779
Oesophageal Candidiasis	0	0.0%	1	1.7%	1	1.1%	2	5.0%	0.513
Oral Candidiasis	0	0.0%	4	6.8%	17	18.1%	3	7.5%	0.118
Pneumocystis Pneumonia	0	0.0%	0	0.0%	1	1.1%	2	5.0%	0.231
Tuberculosis	0	0.0%	2	3.4%	26	27.7%	16	40.0%	<0.001
Varicella Zoster	0	0.0%	1	1.7%	2	2.1%	0	0.0%	0.825
Total Infection Episodes	**0**		**18**		**84**		**42**		<0.0001

4.2.8 Infection Prevalence between those not on HAART and those on HAART

There was no statistical correlation between occurrence of opportunistic infections and whether a child was on HAART or not (p = 0.320) (Table 19).

Table 19: Occurrence of Opportunistic Infections between those not on HAART and those on HAART

On HAART	At least one infection	No Infections	p value
No (n=42)	34 (81.0%)	8 (19.0%)	0.320
Yes (n=154)	134 (87.0%)	20 (13.0%)	
Total (n=196)	**168 (85.7%)**	**28 (14.3%)**	

There was also no statistical significance in variation of prevalence of individual opportunistic infections between those on HAART and those not on HAART (Table 20). For all the opportunistic infections the p value was greater than 0.05.

Table 20: Comparison of Prevalence of Individual Opportunistic Infection between those on HAART and those not on HAART

Opportunistic Infection	Not on HAART (n=42)		On HAART (n=154)		p value
	No.	%	No.	%	
Bacterial Pneumonia	16	38.1%	43	27.9%	0.203
Cryptococcal Meningitis	0	0.0%	3	1.9%	0.362
Herpes Simplex	0	0.0%	1	0.6%	0.601
Kaposi's Sarcoma	1	2.4%	1	0.6%	0.322
Lymphoid Pneumonia	0	0.0%	1	0.6%	0.601
Oesophageal Candidiasis	2	4.8%	2	1.3%	0.159
Oral Candidiasis	2	4.8%	22	14.3%	0.095
Pneumocystis Pneumonia	0	0.0%	3	1.9%	0.362
Tuberculosis	12	28.6%	32	20.8%	0.283
Varicella Zoster	1	2.4%	2	1.3%	0.613
Total Infection Episodes	**34**		**110**		0.507

4.2.9 Comparison of Prevalence of infections by duration on HAART

There was a significant statistical correlation between duration on HAART and occurrence of opportunistic infections (p = 0.020) (Table 21). As duration on HAART increased, the number of persons who had suffered an opportunistic infection decreased.

Table 21: Occurrence of Opportunistic Infections among children with different durations on HAART

Duration on HAART grouped	At least one infection	No Infections	p value
1 Upto 1 year (n=87)	79 (90.8%)	8 (9.2%)	0.020
2 Above 1 years to 2 years (n=37)	34 (91.9%)	3 (8.1%)	
3 Above 2 years to 3 years (n=22)	15 (68.2%)	7 (31.8%)	
4 Above 3 years (n=8)	6 (75.0%)	2 (25.0%)	
Total number of children on HAART (n=154)	**134 (87.0%)**	**20 (13.0%)**	

Duration on HAART correlated significantly with prevalence of tuberculosis (p = 0.010) (Table 22). Cases of tuberculosis decreased as duration on HAART increased and no cases were found in those who had been on HAART for more than 2 years.

The total number of infection episodes also had a significant statistical correlation with the duration on HAART (p < 0.001). Number of infection episodes decreased with increasing duration on HAART.

Table 22: Comparison of Prevalence of Individual Opportunistic Infection by duration on HAART

	Upto 1 year (n=87)		Above 1 years to 2 years (n=37)		Above 2 years to 3 years (n=22)		Above 3 years (n=8)		P
Opportunistic Infection	No.	%	No.	%	No.	%	No.	%	values
Bacterial Pneumonia	31	35.6%	9	24.3%	2	9.1%	1	12.5%	0.054
Cryptococcal Meningitis	3	3.4%	0	0.0%	0	0.0%	0	0.0%	0.502
Herpes Simplex	0	0.0%	1	2.7%	0	0.0%	0	0.0%	0.364
Kaposi's Sarcoma	1	1.1%	0	0.0%	0	0.0%	0	0.0%	0.855
Lymphoid Pneumonia	1	1.1%	0	0.0%	0	0.0%	0	0.0%	0.855
Oesophageal Candidiasis	2	2.3%	0	0.0%	0	0.0%	0	0.0%	0.668
Oral Candidiasis	17	19.5%	2	5.4%	1	4.5%	2	25.0%	0.079
Pneumocystis Pneumonia	2	2.3%	1	2.7%	0	0.0%	0	0.0%	0.858
Tuberculosis	25	28.7%	7	18.9%	0	0.0%	0	0.0%	0.01
Varicella Zoster	0	0.0%	2	5.4%	0	0.0%	0	0.0%	0.093
Total Infection Episodes	**82**		**22**		**3**		**3**		<0.001

4.3 Prescription Errors identified in Medicines Prescribed

One hundred and twelve prescription errors were identified most of which were due to incorrect dosage (93.8%) (Table 23). Cotrimoxazole had the highest number of wrong doses prescribed, followed by Efavirenz and Lamivudine.

Table 23: Prescription Errors identified in Medicines Prescribed

Drug	Inappropriate Choice	Incorrect Dosage	Interaction Present	Contraindication Present
Abacavir	0	2	0	0
Amoxicillin	1	0	0	0
Appevita®	1	0	0	1
Cotrimoxazole	1	48	0	1
Didanosine	0	2	0	0
Efavirenz	0	13	0	0
Erythromycin	1	0	0	0
Fluconazole	0	1	0	0
Griseofulvin	0	1	0	0
Lamivudine	0	13	0	0
Lopinavir/ritonavir	0	3	0	0
Nevirapine	0	9	0	1
Stavudine	0	2	0	0
Zidovudine	0	11	0	0
Total	**4 (3.6%)**	**105 (93.8%)**	**0 (0.0%)**	**3 (2.7%)**

4.4 Availability of prescribed medicines in the CCC Pharmacy

A total of one thousand and thirty drug-prescriptions were reviewed in the study (Table 24). Antiretrovirals (44.6%), antibiotics (25.4%) and vitamin supplements (18.5%) were the most prescribed drugs.

Majority of drugs prescribed (86.9%) were available at the CCC Pharmacy but anthelmintics and haematinics were not available.

Table 24: Availability of prescribed medicines in the CCC Pharmacy

DRUG CATEGORY	Number of times Prescribed	Available	Unavailable
1. Antacid	1(0.1%)	1(100.0%)	0(0.0%)
2. Analgesics	18(1.7%)	18(100.0%)	0(0.0%)
3. Antibiotics	262(25.4%)	225(85.9%)	37(14.1%)
4. Antifungals	20(1.9%)	15(75.0%)	5(25.0%)
5. Anthelmintics	9(0.9%)	**0(0.0%)**	9(100.0%)
6. Antihistamines	16(1.6%)	11(68.8%)	5(31.3%)
7. Antiretrovirals	459(44.6%)	459(100.0%)	0(0.0%)
8. Antispasmodics	1(0.1%)	1(100.0%)	0(0.0%)
9. Corticosteroids	3(0.3%)	2(66.7%)	1(33.3%)
10. Cough Syrups	25(2.4%)	2(8.0%)	23(92.0%)
11. Haematinics	12(1.2%)	**0(0.0%)**	12(100.0%)
12. Topical Preparations	13(1.3%)	1(7.7%)	12(92.3%)
13. Vitamin Supplements	191(18.5%)	160(83.8%)	31(16.2%)
TOTAL	**1030(100%)**	**895(86.9%)**	**135(13.1%)**

5.0 DISCUSSION

5.1 Prevalence of Opportunistic Infections

Twenty eight children presented with an opportunistic infection during the study period thus the point prevalence of opportunistic infections among the children was 14.3%. This is slightly lower than the initial anecdotal estimate of 15% prevalence. The difference may not represent a true reduction in infection prevalence as the initial estimate was not based on any study and may have been erroneous. However, it is expected that there should be a reduction in infection prevalence among the HIV infected children following scale-up in antiretroviral therapy initiation and increased uptake of infection chemoprophylaxis.

Eighty nine (45.4%) children in the study were aged 5 years and below which was the most common age-group while those aged above 15 years were only 7 (3.6%). This implies that most of the children receiving out patient HIV care services at Kenyatta National Hospital CCC are within this age group. The overall mean age was found to be 6.7 years.

Children aged 5 years and below are generally immunologically naïve and vulnerable to opportunistic infections. Indeed, 94 (48.0%) children in the study were in Clinical WHO Stage 3 indicating significant immunosuppression and there was need for aggressive prevention and treatment of opportunistic infections. It was also found that majority of the patients (85.7%) had suffered at least one opportunistic infection episode in the past 12 months indicating significant infection burden in the population.

Occurrence of opportunistic infections was found to correlate significantly with age group where more children aged 10 years or below (90.9%) had suffered at least one infection compared to those above 10 years (66.7%). It was however noted that children aged 10 years and above were much fewer than those below 10 years. Bearing in mind the fact that mother-to-child transmission of HIV accounts for over 95% of childhood paediatric infections in sub-Saharan Africa it would be assumed that most of the children got infected early in life. Thus, a possible explanation for the low number of older children would be some having succumbed to HIV-associated illnesses leaving those with relatively stronger immunity. These would therefore be better resistant to opportunistic infections compared to their younger counterparts. Indeed, children in WHO Stage 1 were slightly older with those in WHO Stage 4 being younger.

The commonest opportunistic infections were found to be bacterial pneumonia, tuberculosis and oral candidiasis. These have been observed to be common clinical manifestations in paediatric HIV infection (31, 32). The pathogenesis of HIV disease is based on the interrelationship between HIV and the host immune system [59]. Studies suggest that immunopathogenesis is a result of defective T cell homeostasis. Progressive and severe depletion of CD4 helper lymphocyte impairs cell-mediated immunity leaving the host open to infections with intracellular pathogens such us *Mycobacterium*, whilst the co-existing antibody abnormalities predispose to infections with encapsulated bacteria e.g. *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*.

In this study, there was no significant association between prevalence of the various opportunistic infections and age group. This agrees with a study conducted in India to determine the various clinical manifestations of HIV infection in children as per their age [60]. The study found that there was no significant difference among the age groups.

There was a significant positive correlation between occurrence of opportunistic infections and WHO Stage with percentage of those who had suffered an opportunistic infection increasing with 'increasing' WHO Stage ($P < 0.001$). WHO Stage also correlated significantly with the prevalence of bacterial pneumonia ($P < 0.01$) and tuberculosis ($P < 0.001$). The prevalence of both infections increased with deteriorating WHO stage. Staging is a standardised method for assessing HIV disease progression and for making treatment decisions [3, 63]. WHO Paediatric Clinical staging is one of two international clinical staging systems that classify the severity of HIV infection in children, the other being the U.S. CDC Clinical staging. WHO staging divides HIV-infected children into four categories Stage 1, Stage 2, Stage 3 and Stage 4 in order of increasing HIV disease severity. It therefore follows that infection prevalence of opportunistic infections will increase with 'increasing' WHO stage as seen with bacterial pneumonia and tuberculosis in this study.

Even though children in Stage 1 were slightly older (mean age 8.31 years) while those in Stage 4 were slightly younger (mean age 6.14 years), the difference in the years is so small that age can not be said to have contributed to the difference in opportunistic infection prevalence among the WHO Stages.

No correlation was found between occurrence of opportunistic infections and HAART initiation. This means that both the child on HAART and one not initiated on HAART had an equal chance of acquiring an opportunistic infection. This may be because those not yet on HAART are generally those who are immunocompetent and not clinically nor immunologically eligible. For a child to be considered eligible for HAART they are assessed by clinical criteria (WHO Stage 3 or 4) and/or need to be below a certain CD4% depending on their age [3].

HAART describes a combination of antiretroviral drugs into a regimen potent enough to drastically reduce viral replication and prevent the emergence of resistance. Such regimens, which are combinations of at least three ARV drugs, have been associated with immunologic restoration, slower HIV disease progression, durable therapeutic responses, improvements in quality of life, and reduction in the emergence of drug resistance

As duration on HAART increased the number of opportunistic infections were found to drop significantly ($P = 0.020$). Cases of tuberculosis decreased as duration on HAART increased. In fact, no cases of tuberculosis were found in those who had been on HAART for more than two years. It is expected that the longer one has been on HAART, in the absence of development of resistance, the better their immunity and hence ability to prevent infection. However, since age correlated significantly with duration on HAART ($P = 0.004$), such that the older children had been on HAART longest, age may have contributed to the reduction in number of opportunistic infections. Older children would have better intrinsic immunity than the younger ones.

5.2 Prescription Errors identified in Medicines Prescribed

Proper and adequate pharmacovigilance is often reported to be lacking in children's drug therapy, especially in developing countries. This means that children are at risk of developing adverse reactions to drugs as a result of medication errors.

In this study 112 prescription errors were identified, most of which were due to incorrect dosage 105 (93.8%). There were 4 (3.6%) cases of inappropriate choice and 3 (2.7%) cases of contraindications. No drug-drug, drug-disease or drug-patient interactions were observed.

The frequency of medication errors in this study agrees with various studies which have been done to identify and correct medication errors most frequently committed in paediatric outpatient prescriptions. A study conducted at the Lagos State University Teaching Hospital on medication errors in paediatric outpatient prescriptions found dosing errors to be commonest with errors of underdosing and overdosing being associated with 38.0% and 18.8% drugs respectively [46].

The incorrect doses were mostly underdosage. Cotrimoxazole, which was mostly prescribed for chemoprophylaxis, had the highest number of incorrect doses for a single drug (45.7%). The clinicians at the CCC have been provided with 2 ways for determining the dose of prophylactic cotrimoxazole namely; a) Calculation at 5 mg/kg of trimethoprim once given daily, or b) Use of dosing charts (weight bands). The 48 cases of incorrect cotrimoxazole doses did not follow either of these two ways and the doses were mostly below recommended. It may be that the clinicians did not recalculate the doses during the clinic visit but just continued with that which had been prescribed earlier ignoring the fact that the child was growing hence increasing in weight.

Incorrect dosage of antiretrovirals constituted 52.4% of dosage errors the commonest being dosing of Efavirenz and Lamivudine. The most common factors associated with errors in dosing of antiretrovirals have been found to be confusion/lack of familiarity regarding appropriate dosing frequency (30.3%) or dosage (25.5%), and confusion due to need for multiple dosage units per dose (13%) [61]. It seemed that some prescribers at KNH CCC were not familiar with the appropriate dosage of paediatric antiretrovirals. The need to calculate the doses by mg/kg body weight or mg/m^2 at each visit is considered a challenge by many clinicians who find it tedious. Dosing charts have been developed to assist in determination of appropriate doses based on weight bands.

Incorrect dosage results in either subtherapeutic (in underdosing) or toxic (in overdosing) blood levels of the drug. Subtherapeutic levels pose the risk of treatment failure and even development of resistance which may result in prolongation of duration of treatment, need for hospitalization and even death. Underdosing of antiretrovirals was of particular concern due to the risk of treatment inadequacy and failure as a result of development of viral resistance.

Concurrent prescribing of Appevita® and multivitamin syrup which is prescription of 2 similar medications was considered an inappropriate choice and a contraindication. This error could be attributed to lack of familiarity by the clinicians to the contents of the preparations and calls for the attending pharmacist to educate the prescribers to avoid recurrence of the error. Co-administration of similar drugs may result in overdosage and toxicity.

prescribing of erythromycin and amoxicillin with no indication (infection) documented in the file was also considered inappropriate choice (2 counts) though this may have been an omission by the clinician.

Another contraindication was as a result of prescribing cotrimoxazole to a child known to be allergic. (This was even written on the cover of the patient's file). This also constituted inappropriate choice. Administration of cotrimoxazole to a patient with known hypersensitivity has been known to result in severe adverse reactions involving the skin and mucous membranes and should be avoided. The CCC pharmacy does not store patients' allergy information and therefore may not able to intercept in such cases.

The third contraindication involved prescribing of nevirapine to a child who received a single dose at birth for prevention of mother to child HIV transmission (PMTCT). The national HIV treatment guidelines require that single-dose Nevirapine (SDNVP) exposed babies be started on NNRTI-sparing HAART. This is due to the low barrier to resistance of Nevirapine that results in development of HIV resistance after administration of single dose as in PMTCT. Cross resistance is known to exist between Nevirapine and Efavirenz hence they are to be avoided in treatment of SDNVP exposed babies. The error may have been due to lack of familiarity with this guideline or not noticing in the patient file the fact that the child got the single dose Nevirapine at birth.

Studies have demonstrated that medication errors are usually preventable and those most commonly implicated in the harmful or potentially harmful preventable events, and hence the

best targets for prevention, are dosing errors, particularly during prescribing [53]. The causes of medication errors are usually multifactorial and it is important that when investigating medication errors, particular focus should be placed on system changes. In KNH CCC, it was noted that the pharmacy staff often disregarded the prescribed dose and dispensed to patients according to their own dosing charts. This gave the impression that prescribing errors are so common that the pharmacy staff have decided to disregard the prescribed doses and instead to dispense in accordance to the pharmacy ARV dosing charts. This is a risky practice as the prescribers are not informed or consulted on the changes.

Medication errors identified in a study of prescribing practices of doctors attending to under fives in a children's outpatient clinic in Owerri, Nigeria led to suggestion of interventions such as developing and circulating easy to use treatment guidelines for diseases commonly seen in the centre, a regular audit of the application of these guidelines and institution of continuing medical education of doctors on rational drug use and evidence based medicine [54]. At the KNH CCC there were no treatment guidelines for prescribers nor antiretroviral dosing charts at the time of the study. Continuing medical education sessions are conducted once in a while but none has been done on rational drug use.

Active involvement of pharmacists has been shown to drastically reduce medication errors [62]. The duration of prescribing errors was decreased when a clinical pharmacist monitoring patients receiving HAART intervened to resolve errors. The clinical pharmacist was able to offer quick intervention in correcting the errors. Currently at the KNH CCC, medicines are dispensed by a pharmaceutical technologist employed on part-time basis who may be limited in knowledge with

regard to drug dosing and interactions. Also they may feel intimidated by the prescribers and hence not contact them when a prescribing error is noted and prefer to instead dispense based on the pharmacy dosing charts. A pharmacist based at the clinic would be able to consult with the prescribers on perceived prescription errors and even peruse the files for relevant patient information.

5.3 Availability of prescribed medicines in the CCC Pharmacy

Whereas antiretroviral medicines are provided free of charge to HIV infected patients through the Global Fund and President's Emergency Plan for AIDS Relief (PEPFAR) programs, patients have to purchase drugs for other intercurrent infections. Many of the drugs needed to treat the opportunistic infections present during advanced HIV infection and AIDS are prohibitively expensive for both developing countries and most individuals in those countries.

One strategy to contain the cost of drugs is for governments to develop and implement an integrated national drug policy based upon the concept of essential drugs and their rational use [56].

In the KNH CCC selected drugs for opportunistic infections are purchased through donation by the University of Nairobi AIDS Care and Treatment Services (ACTS) project. The funds are limited and therefore limit the range of drugs that can be procured. The majority of drugs prescribed (86.9%) were available at the CCC Pharmacy though anthelmintics and haematinics were not available during the entire period of the study. Important (essential) prescribed medicines that were not available or whose availability was erratic included albendazole,

Ascoril®, coamoxiclav, dapsone, erythromycin, griseofulvin, multivitamin, nystatin, povidone iodine mouthwash, pyridoxine, Ranferon®, RH, RHZ, salbutamol and tetracycline eye ointment.

There is therefore the possibility of patients not obtaining the medicines due to the associated costs resulting in deterioration which may result in increased morbidity and mortality. It may be imperative for the CCC to request for increased funding for procurement of required medicines and also to seek out support and partnership with organizations that are able to offer donations.

5.4 Limitations of the Study

- Reliance on clinician's diagnosis of infection – this meant that if a condition was not correctly diagnosed it may have been mis-counted.
- Omitted/missing information in patient's file – information that was not written in the patients' file could not be obtained.
- Financial resources – financial limitation restricted duration and design of study as well as expenditure in statistical analysis.
- Time – led to restricted amount of information the study could collect and analyse.

6.0 CONCLUSION

The prevalence of OIs in HIV-infected children varies with pathogen, duration on HAART and WHO Stage. The most common infections among the HIV-infected children at KNH CCC are readily treatable and/or preventable, with most of their treatments being simple and available. Incorrect dosage of cotrimoxazole and antiretrovirals is the most common prescription error.

Recommendations

- Discussion among CCC prescribers and pharmacists on medication errors should be encouraged with an aim of identifying underlying factors and developing strategies to prevent them.
- The paediatric prescriptions should be routinely reviewed at the pharmacy for appropriateness, adequacy and dosage accuracy using the patient's weight, age, and other appropriate indicator(s) before dispensing and/or refill.
- Patient files should be forwarded to the CCC pharmacy to enable the staff obtain key patient information such as allergies, single-dose Nevirapine exposure etc., in order to be able to intervene when an inappropriate prescription is raised.
- Deployment of a full-time suitably qualified pharmacy staff who would be confident to work with prescribers and discuss medication errors as they arise.
- Rational drug prescription should form part of continuous medical education.
- There should be continued infection prevalence and prescription surveillance to guide medicine procurement by prioritizing essential, commonly prescribed medicines.
- The CCC should seek for additional or supplementary funding to facilitate procurement of all essential medicines.

Future Work

- Study of factors underlying medication errors in prescribing to paediatric patients at the KNH CCC.
- Study of natural history of HIV and incidence of opportunistic infections in HIV-infected children.

7.0 REFERENCES

1. UNAIDS. Paediatric HIV/AIDS: Point of VIEW September 2002.
2. Kenya Demographic and Health Survey. Ministry of Health. Government of Kenya, 2003.
3. Tindyebwa D, Kayita J, Musoke P, *et al.* Handbook on Paediatric AIDS in Africa; The African Network for the Care of Children Affected by AIDS (ANECCA), 2006.
4. NASCOP, Ministry of Health, Kenya. Guidelines for Antiretroviral Therapy in Kenya 4th Edition, 2007.
5. Chiappini E, Galli L, Tovo PA, *et al.* Changing patterns of clinical events in perinatally HIV-1 infected children during the era of HAART. AIDS. 2007;21(12):1607-15.
6. World Health Organisation. Antiretroviral Therapy of HIV infection in Infants and Children in Resource-limited Settings, Towards Universal Access: Recommendations for a Public Health Approach (2006 revision).
7. Nesheim SR, Kapogiannis BG, Soe MM, *et al.* Trends in opportunistic infections in the pre- and post-highly active antiretroviral therapy eras among HIV-infected children in the Perinatal AIDS Collaborative Transmission Study, 1986-2004. Pediatrics. 2007;120(1):100-9.
8. Gortmaker SL, Hughes M, Cervia J, *et al.* Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. N Engl J Med 2001;345:1522–8.
9. Lindegren ML, Steinberg S, Byers RH. Epidemiology of HIV/AIDS in children. Pediatr Clinics North Am 2000;47:1–20.
10. World Health Organization. Nairobi Declaration. 1988.
11. Kaushal R. Medication errors and adverse drug events in pediatric inpatients. Journal of the American Medical Association, 2001, 285:2114-2120.
12. Cohen D. Poverty and HIV/AIDS in Sub Saharan Africa. UNDP Issues Paper No. 27
13. UNAIDS/WHO, 2007 AIDS epidemic update. Geneva, 2007 (http://www.unaids.org/en/KnowledgeCentre/HIVData/EpiUpdate/EpiUpdArchive/2007, accessed 2 July 2008).

14. World health statistics 2008. Geneva, World Health Organization, 2008 (http://www.who.int/healthinfo/statistics/en, accessed 2 July 2008).
15. United Nations General Assembly. Political Declaration on HIV/AIDS. New York, United Nations, 2006 (United Nations General Assembly document 60/262; http://www.unaids.org/en/AboutUNAIDS/Goals/UNGASS, accessed 2 July 2008).
16. United Nations Millennium Development Goals. New York, United Nations, 2001 (http://www.un.org/millenniumgoals, accessed 2 July 2008).
17. Yeung LTF, King SM, Roberts EA. Mother-to-infant transmission of hepatitis C virus. Hepatology 2001;34:223–9.
18. Kovacs A, Schulchter M, Easley K, *et al.* Cytomegalovirus infection and HIV-1 disease progression in infants born to HIV-1-infected women. N Engl J Med 1999;341:77–84.
19. Gutman LT, Moye J, Zimmer B, Tian C. Tuberculosis in human immunodeficiency virus-exposed or infected United States children. Pediatr Infect Dis J 1994;13:963–8.
20. Ylitalo N, Brogly S, Hughes MD, *et al.* Risk factors for opportunistic illnesses in children with human immunodeficiency virus in the era of highly active antiretroviral therapy. Arch Pediatr Adolesc Med. 2006;160(8):778-87.
21. World Health Organization, Geneva. Nutrient requirement for people with HIV and AIDS. Report of a technical consulation. May 2003.
22. Babirekere-Iriso E, Musoke P, Kekitiinwa A. Bacteraemia in severely malnourished children in an HIV-endemic setting. Ann Trop Paediatr. 2006;26(4):319-28.
23. de Onis, M, Frongillo EA, Blossner M. Is malnutrition declining? An analysis of changes in levels of child malnutrition since 1980.*Bull WHO 2000*; 78 (10): 1222-33.
24. Gorbach SL, Tamsin AK, and Roubenoff R. Interactions between nutrition and infection with human immunodeficiency virus. *Nutr Rev* 1993; 51: 226-234.
25. Scrimshaw NS and SanGiovanni JP. Synergism of nutrition, infection and immunity: an overview. *Am J Clin Nutr* 1997; 66: 464S-477S.
26. Beisel WR. Nutrition and immune function: Overview. *J Nutr* 1996; 126(10): 2611-2615.
27. Wheeler DA, Gilbert CL, Launer CA *et al.* Weight loss as a predictor of survival and disease progression in HIV infection. *J Acquir Immune Defic Syn* 1998; 18: 80-85.
28. Kotler D, Tierney AR, Wang J, Pierson RN. Magnitude of body cell mass depletion and the timing of death from wasting in AIDS. *Am J Clin Nutr* 1989; 50: 444-447.

29. Suttmann U, Ockenga J, Selberg O *et al.* Incidence and prognostic value of malnutrition and wasting in human immunodeficiency virus-infected outpatients. *J Acquir Immune Defic Syn* 1995; 8: 239-246.
30. Agarwal D, Chakravarty J, Sundar S. Correlation between clinical features and degree of immunosuppression in HIV infected children. Indian Pediatr. 2008;45(2):140-3.
31. Dhurat R, Manglani M, Sharma R, et al. Clinical spectrum of HIV infection. Indian Pediatr. 2000;37(8):831-6.
32. Madhivanan P, Mothi SN, Kumarasamy N, *et al.* Clinical manifestations of HIV infected children. Indian J Pediatr. 2003;70(8):615-20.
33. Moore RD, Chaisson RE. Natural history of opportunistic disease in an HIV-infected urban clinical cohort. Ann Intern Med. 1996;124(7):633-42.
34. Dankner WM, Lindsey JC, Levin MJ, and the Pediatric AIDS Clinical Trials Group Protocol Teams 051, 128, 138, 144, 152, 179, 190, 220, 240, 245, 254, 300 and 327. Correlates of opportunistic infections in children infected with the human immunodeficiency virus managed before highly active antiretroviral therapy. Pediatr Infect Dis J 2001;20:40–8.
35. Gona P, Van Dyke RB, Williams PL, *et al.* Incidence of opportunistic and other infections in HIV-infected children in the HAART era. JAMA. 2006 Jul 19;296(3):292-300.
36. Ledergerber B, Egger M, Erard V, *et al.* AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. JAMA. 1999;282(23):2220-6.
37. Viani RM, Araneta MR, Deville JG,*et al.* Decrease in hospitalization and mortality rates among children with perinatally acquired HIV type 1 infection receiving highly active antiretroviral therapy. Clin Infect Dis. 2004;39(5):725-31. Epub 2004 Aug 16.
38. Jones JL, Hanson DL, Dworkin MS, *et al.* Surveillance for AIDS-defining opportunistic illnesses. 1992-1997. MMWR CDC Surveill Summ. 1999;48(2):1-22.
39. Yazdanpanah Y, Chêne G, Losina E, *et al.* Incidence of primary opportunistic infections in two human immunodeficiency virus-infected French clinical cohorts. Int J Epidemiol. 2001; 30:864-871.

40. NASCOP. Comprehensive Paediatric HIV Care, Kenya National Course Curriculum, 2006.
41. CDC Guidelines for Treating Opportunistic Infections Among HIV-Exposed and Infected Children. MMWR 2004;53 (RR-14); 1-63.
42. CDC Guidelines for Treating Opportunistic Infections Among HIV- Infected Adults and Adolescents MMWR 2004;53 (RR15); 1-112.
43. Walker R, Whittlesea C (2007). Clinical Pharmacy and Therapeutics – 4th Ed. Elsevier Limited. USA. Page 130.
44. Marcia L Buck. Preventing Medication Errors in Children. Pediatric Pharmacotherapy. 1999; 5(10): 1.
45. Koren G, Haslam RH. Pediatric medication errors: predicting and preventing tenfold disasters. J Clin Pharmacol 1994;34:1043-5.
46. Oshikoya KA, Ojo OI. Medication errors in paediatric outpatient prescriptions of a teaching hospital in Nigeria. Nig Q J Hosp Med. 2007;17(2):74-8.
47. Vincer MJ, Murray JM, Yuill A, *et al.* Drug errors and incidents in a neonatal intensive care unit: a quality assurance activity. Am J Dis Child 1989;143:737-40.
48. Jonville AE, Autret E, Bavoux F, *et al.* Characteristics of medication errors in pediatrics. DICP Ann Pharmacother 1991;25:1113-8.
49. Lesar TS. Errors in the use of medication dosage equations. Arch Pediatr Adolesc Med 1998;152:340-4.
50. Rowe C, Koren T, Koren G. Errors by paediatric residents in calculating drug doses. Arch Dis Child 1998;79:56-8.
51. Kirk RC, Li-Meng Goh D, Packia J *et al.* Computer calculated dose in paediatric prescribing. Drug Saf. 2005;28(9):817-24.
52. Lesar TS, Briceland L, Stein DS. Factors related to errors in medication prescribing. JAMA. 1997;277(4):312-7.
53. Kunac DL, Reith DM. Preventable medication-related events in hospitalised children in New Zealand. N Z Med J. 2008;121(1272):17-32.
54. Nwolisa CE, Erinaugha EU, Ofoleta SI. Prescribing practices of doctors attending to under fives in a children's outpatient clinic in Owerri, Nigeria. J Trop Pediatr. 2006;52(3):197-200. Epub 2005 Dec 9.

55. Rojo P. Access to essential drugs in developing countries. Gac Sanit. 2001;15(6):540-5.
56. World Health Organization. Essential drugs and medicines policy © WHO 2008.
57. Kaur SR. Essential drugs in AIDS care: issues of availability and affordability. Health Millions. 1996;22(6):21-2.
58. Smith MK, Tickell S. The essential drugs concept is needed now more than ever. Trans R Soc Trop Med Hyg. 2003;97(1):2-5.
59. Parvin Kumar and Michael Clark. Clinical Medicine – 6th Ed. Elsevier Limited. USA. 2005:130,140.
60. Shah I. Age related clinical manifestations of HIV infection in Indian children. J Trop Pediatr. 2005;51(5):300-3.
61. Purdy BD, Raymond AM, Lesar TS. Antiretroviral prescribing errors in hospitalized patients. Ann Pharmacother. 2000;34(7-8):833-8.
62. Heelon M, Skiest D, Tereso G, *et al*. Effect of a clinical pharmacist's interventions on duration of antiretroviral-related errors in hospitalized patients. Am J Health Syst Pharm. 2007;64(19):2064-8.
63. World Health Organization, WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-related disease in Adults and Children, 2006.

8.0 APPENDICES

APPENDIX 1: SAMPLE DATA COLLECTION FORM

Date .....

Study No. .....

1. Patient Biodata

Age _____ Sex _____

2. Background Clinical Information

Current WHO stage I [ ] II [ ] III [ ] IV [ ]
HAART started Y [ ] N [ ] Duration on HAART _____

3. Occurrence of Opportunistic Infection(s)

Opportunistic Infection	Current Tick [√]	In the past 12 months Tick [√]
Bacterial pneumonia		
Cryptococcal meningitis		
Esophageal Candidiasis		
Herpes simplex		
Kaposi's sarcoma		
Lymphoid interstitial pneumonia		
Oral Candidiasis		
Pneumocystis jiroveci pneumonia		
Tuberculosis		
Varicella zoster		

4. Evaluation of Medication Prescribed

Drug Name	Drug Choice (tick if appropriate)	Dosage (tick if appropriate)	Interactions (tick if present)	Contraindications (tick if present)	Available in CCC Pharmacy

APPENDIX 2: KNH ERC APPROVAL

20/02/08
Allowed to carry out
research in CCC

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/ 01/ 183

15th February 2008

Dr. Mutua Susan Awino
Dept. of Pharmaceutics and Pharmacy Practice
School of Pharmacy
University of Nairobi

Dear Dr. Mutua

RESEARCH PROPOSAL: "PREVALENCE AND MANAGEMENT OF INFECTIONS IN HIV-INFECTED CHILDREN" (P363/12/2007)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** your revised research proposal for the period 15th February 2008 – 14th February 2009.

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 specimen must also be obtained from KNH-ERC for each batch.

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

This information will form part of database 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-ERC

c.c. Prof. K.M. Bhatt, Chairperson, KNH-ERC
The Deputy Director CS, KNH
The Dean, School of Pharmacy, UON
The Chairman, Dept. of Pharmaceutics and Pharmacy Practice, UON
Supervisor: Dr. David Scott, Dept. of Pharmaceutics & Pharmacy Practice,UON

APPENDIX 3: TABLE OF TREATMENT GUIDELINES

NASCOP PAEDIATRIC HIV CURRICULUM[40]	ANNECCA[3]	WHO	CDC[42]
1. TUBERCULOSIS			
Isoniazid 5 –10 mg/kg/d (max 300mg) Rifampicin 10-15 mg/kg/d Pyrazinamide 25 – 35 mg/kg/d (2 months) Ethambutol 55-25mg/kg/d (max 2.5g) children > 8 yrs 6 month treatment recommended Add prednisone (4 mg/kg OD x 6 weeks) in TBM, miliary TB, massive pleural effusion and Pericarditis **Chemoprophylaxis** This should be given to the following: ▪ Neonate whose mother is diagnosed with PTB ▪ All contacts under 5 years of age in a household with an adult with open TB ▪ Need to first exclude active TB disease INH 5-10mg/kg/day for 6 months	**Smear-Negative Pulmonary TB or Non-severe Disease** First 2 months: Isoniazid + Rifampicin + Pyrazinamide daily or 3 times a week Followed by either Next 6 months: Isoniazid + Ethambutol **or** Isoniazid + Thioacetazone daily **or** Next 4 months: Isoniazid + Rifampicin daily or 3 times a week **Smear-Positive Pulmonary TB or Severe Disease** First 2 months: Isoniazid + Rifampicin + Pyrazinamide + Streptomycin (or ethambutol) daily or 3 times a week Followed by either Next 6 months: Isoniazid + Ethambutol **or** Isoniazid + Thioacetazone daily **or** Next 4 months: Isoniazid + Rifampicin daily or 3 times a week **Meningitis, Miliary TB or Spinal TB with Neurologic Signs (regardless of Smear results)** First 2 months: Isoniazid + Rifampicin + Pyrazinamide + Streptomycin (or ethambutol) daily or 3 times a week Next 7 months: Isoniazid + Rifampicin		Initial empiric treatment of active disease (induction phase) should generally consist of a 4-drug regimen (iso-niazid, rifampin, pyrazinamide, and either ethambutol or streptomycin). Following the 2-month induction phase, for treatment of *M. tuberculosis* known to be sensitive to isoniazid and rifampin, therapy is continued with isoniazid and rifampin to complete therapy.

	Daily Dosing Isoniazid 5mg/kg (range 4-6) Rifampicin 10mg/kg (range 8-12) Pyrazinamide 25mg/kg (range 20-30) Ethambutol 15mg/kg (range 15-20) Streptomycin 15mg/kg (range 12-18) **Chemoprophylaxis (after active TB is excluded)** ▪ Infants born to HIV-infected women diagnosed with TB disease who started treatment < 2 months before delivery ▪ Infants and children with exposure to an adult with active TB disease INH 5-10mg/kg orally once daily for 6 months		
2. PNEUOCYSTIS JIROVECII PNEUMONIA			
Cotrimoxazole I.V Trimethoprim (TMP): 15-20 mg/kg/day in 3-4 doses Sulphamethoxazole (SMX): 75-100mg/kg/day in 3-4doses Infuse each dose over one hour After acute symptoms subside, change from I.V. to oral If I.V. formulation not available, give oral form Give for total of 21 days OR IV Pentamidine 4mg/kg/day OD Course: 21 days Add prednisone 2mg/kg for 7-14 days in severely ill children **Prophylaxis** Cotrimoxazole (TMP-SMZ) 24 - 30mg/kg/day p.o once daily OR SMX 20-25 mg/kg once dailyTMP 4-5 mg/kg once	**I.V. Cotrimoxazole** Trimethoprim (TMP): 20mg/kg/d OR 80mg/kg/d of Sulphamethoxazole (SMX) given every 6 hours for 21 days Give same dose orally if IV preparations are not available. Add prednisone 2mg/kg/d for 7-14 days if child is in severe respiratory distress (taper if treatment > 7 days). **Follow-Up** **After an acute episode of PCP, provide daily** cotrimoxazole 10mg/kg/day of TMP, orally. This secondary prophylaxis is life-long.	TMP/SMX 15 –20 mg/kg/day of TMP in 3 –4 divided doses in a 21-day course	Trimethoprim/sulfamethoxazole (TMP/SMX): The dose for HIV-infected children aged >2 months is 15–20 mg/kg body weight/day of the TMP component (75–100 mg/kg of SMX component) administered intravenously in 3–4 divided doses, with the dose infused over 1 hour for 21 days. After the acute pneumonitis has resolved, children with mild to moderate disease who do not have malabsorption or diarrhea can be administered oral treatment with the same dose of TMP/SMX in 3–4 divided doses to complete a 21–day course. Pentamidine isothionate (4 mg/kg/day once daily administered intravenously over 60–90 minutes) is recommended for patients

daily) OR Dapsone 2mg/kg p.o daily			intolerant of TMP/SMX or who demonstrate clinical treatment failure after 5–7 days of TMP/SMX therapy.
3. CANDIDIASIS			
– *Local treatments* – *Fluconazole* – *Ketoconazole*	**Oral Candidiasis** ▪ Nystatin 1-2 million U/day divided every 6 hours until resolution **Oesophageal Candidiasis** ▪ Fluconazole 3-6mg/kg once daily or ▪ Amphotericin B 0.3mg/kg/d	**Oral andidiasis** Clotrimazole oral troches 10 g,or Nystatin 400,000 – 600,000 units 5 times daily for 7 –14 days,or oral fluconazole 3 –6 mg/kg once daily for 7 –14 days **Esophageal andidiasis** Oral fluconazole 3 –6 mg/kg once daily for 14 –21 days	
4. CRYPTOCOCCAL MENINGITIS			
Initial treatment Amphotericin B 0.4mg/kg for 14 days then Fluconazole 3-6mg/Kg OD X 8 weeks **Maintenance/prophylaxis** Fluconazole 3 mg/kg OD	**Initial treatment** Amphotericin B 0.7-1.0mg/kg/day for 14 days then Fluconazole 400mg/day for a minimum of 10 weeks, then **Maintenance** Fluconazole 200mg/kg	**Induction therapy:** Amphotericin B (0.7 –1.5 mg/kg/day) plus flucytosine (25 mg/kg/dose four times daily)for 2 weeks **Consolidation therapy:** Fluconazole 5 –6 mg/ kg/dose twice daily for 8 weeks. **Maintenance therapy:** Fluconazole 3 –6 mg/kg/day	
5. TOXOPLASMOSIS			
Pyrimethamine/sulfadiazine (Fansidar, metakelphin) ▪ Pyrimethamine 2mg/kg/d for 3 days, followed by 1mg/kg/d for 12 months ▪ Give daily folinic acid supplement to minimise hematologic toxicity ▪ Sulfadiazine 50mg/kg bid for 12 months ▪ Alternative for sulfa-allergic patients: Clindamycin 5mg/kg qid **Prophylaxis** As PCP	▪ Pyrimethamine loading dose 2mg/kg/d (max 50mg) for 2 days then maintenance 1mg/kg/day (max 25mg plus ▪ Sulfadiazine 50mg/kg q12h plus folinic acid 5-20mg 3 times weekly. Treat until 1-2 weeks beyond resolution of signs and symptoms.		Pyrimethamine (loading dose of 2 mg/kg body weight/day for 2 days, then 1 mg/kg/day for 2–6 months, followed by 1 mg/kg administered three times a week) combined with sulfadiazine (50 mg/kg/dose twice daily), with supplemen-tary leucovorin (folinic acid) for 12 months.
6. HERPES SIMPLEX VIRUS TYPRES 1 & 2 (HSV 1 & 2)			
Severe disease (encephalitis, neonatal,	▪ **IV** Acyclovir 20mg/kg given 3	**HSV gingivostomatitis:** oral acyclovir 20	

disseminated) ▪ **IV** Acyclovir 10mg/kg given 3 times a day for 21 days Mild-moderate disease (localised e.g. Gingivostomatitis) **Oral** acyclovir 20mg/kg 3 times a day for 21 days	times a day for 21 days	mg/kg/dose three times daily or IV acyclovir 5 –10 mg/kg/dose three times daily for 7-14days **Disseminated HSV or encephalitis**: Intravenous acyclovir 10 mg/kg/dose or 500mg/m 2 /dose three times daily for 21 days	
7. VARICELLA ZOSTER VIRUS			
Severe cases: ▪ Admit to hospital ▪ Give IV acyclovir 30mg/kg/day divided 8 hourly for 7 days, or 2 days after cessation of new lesions, whichever is longer ▪ Pain relief, prevention of secondary bacterial infection of lesions **Prophylaxis** Susceptible children who have been exposed to varicella zoster / chicken pox can be given prophylaxis using Varicella-zoster immunoglobulin (VZIG) 125 U per 10 kg (max 625 U) within 48-96 hours of exposure	Severe cases: ▪ Admit to hospital ▪ Give IV acyclovir 30mg/kg/day divided 8 hourly for 7 days, or 2 days after cessation of new lesions, whichever is longer ▪ Pain relief, prevention of secondary bacterial infection of lesions **Prophylaxis** Children who have been exposed to varicella zoster can be given prophylaxis using Varicella-zoster immunoglobulin (VZIG) 125 U per 10 kg (max 625 U) within 48-96 hours of exposure	**Primary varicella infection:** intravenous acyclovir 10 mg/kg/ dose or 500 mg/m 2/dose three times daily for 7 days in children with moderate to severe immunosuppresion.A n oral ormulation should be used only in a child with ild immunosup-pression. **Herper zoster:** Oral acyclovir 20 mg/ kg/dose four times daily (max 800 mg/dose)for 7 days	
8. CYTOMEGALOVIRUS			
Ganciclovir 7.5-10mg/kg/d b.d	Intravenous Ganciclovir 10mg/kg/d in 2-3 divided doses for 2-3 weeks Forscarnet 180mg/kg/d in 3 divided doses for 14 to 21 days may be used when there is sight threatening CMV retinitis.	Intravenous ganciclovir 5 mg/kg/dose twice daily for 14 –21 days followed by lifelong maintenance therapy	
9. BACTERIAL PNEUMONIA			
Treatment is the same as in HIV negative children but duration may need to be longer **Prevention** ▪ Immunization-pneumococcal vaccine ▪ Cotrimoxazole	**Mild Pneumonia (Out-patient management)** Follow recommended national guidelines or IMCI guidelines, if there are no guidelines or you're not aware use: Oral amoxycillin or penicillin or cotrimoxazole (CTX) If a child is already on CTX prophylaxis, CTX should not be used unless		Empiric therapy with an extended-spectrum cephalosporin such as ceftriaxone (80–100 mg/kg bodyweight in 1 or 2 divided doses [maximum daily adult dose: 4 g]), cefotaxime (150–200 mg/kg divided into 3 or 4 doses [maximum daily adult dose: 8–10 g]), or cefuroxime (100–150 mg/kg divided into 3 doses

	PCP is suspected. If PCP is suspected use a high dose (see above). **Severe Pneumonia** First line antibiotics include IV chloramphenicol or Ceftriaxone/Cefotaxime, if available Alternatives include ampicililin/Cloxacillin plus Gentamicin if cephalosporins are not available and there is resistance to chloramphenicol		[maximum daily adult dose: 4–6 g]) is reasonable until culture results are avail-able
10. DIARRHOEAL DISEASES			
		Effective ART is he only reatment hat controls ersistent cryptosporidiosis Supportive are includes hydration, correction f electrolyte abnormalities and nutritional supplementation Nitazoxanide is approved or treatment of (age 1 –3 years:100 mg twice daily,age 4 –11 years:200 mg twice daily)	Effective HAART is the recommended treatment for these infections. Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation should be provided. Antimotility agents should be used with caution among young children. No consistently effective therapy is available for either cryptosporidiosis or microsporidiosis, and duration of treatment among HIV-infected persons is uncertain. Certain agents have demonstrated efficacy in decreasing the severity of symptoms among children. Nitazoxanide is approved for treatment of diarrhea caused by *Cryptosporidium* and *Giardia lamblia* among children.
11. MEASLES			
Management should include 2 doses of vitamin A calculated based on the age of the child 50,000 IU if aged < 6 months; 200,000 IU in children aged 12months to 1 year Immunization should be given to HIV infected			

children at 6 months and repeated at 9 months.			
12. SEPTICAEMIA AND MENINGITIS			
Treatment should follow local guidelines Treatment failure is more frequent. Prevention: immunisation (Hib, pneumococcal)			
13. MAC		ART should be provided to restore immune function Treatment with at least 2 drugs:clarithromycin 7.5 –15 mg/kg twice daily (max 500 mg/dose) plus ethambutol 15 –25 mg/kg/day once daily (max 1 g/dose) Consider adding a third drug,e.g.amikacin or ciprofloxacin in severe cases Duration of treatment: at least 12 months	Initial empiric therapy should include at least two drugs: clarithromycin or azithromycin plus ethambutol. Certain specialists use clarithromycin as the preferred first agent, reserving azithromycin for patients with substantial intolerance to clarithromycin or when drug interactions with clarithromycin are a concern. Rifabutin can be added as a third drug to the clarithromycin/ethambutol regimen, particularly in patients with more severe symptoms or disseminated

APPENDIX 4: WHO CLINICAL STAGING FOR HIV-INFECTED INFANTS AND CHILDREN AGED ≤ 12 YEARS

STAGE I	Asymptomatic Persistent generalized lymphadenopathy (PGL)
STAGE II	*Unexplained*[a] persistent hepatosplenomegaly Papular pruritic eruptions Seborrheic dermatitis Fungal nail infections Angular cheilitis Linear gingival erythema Extensive wart and/or molluscum infection (>5% of body area/face) Recurrent oral ulcerations (>2 episodes/g mos) Parotid enlargement Herpes zoster (>1 episode/12 mos) Hepatosplenomegaly Recurrent or chronic upper respiratory infection (URI): otitis media, tonsillitis, otorrhea, sinusitis (>2 episodes/6 mos)
STAGE III	*Unexplained* moderate malnutrition (-2SD or Z score) not responding to standard therapy *Unexplained* persistent diarrhea (>14 days) *Unexplained* persistent fever (intermittent or constant, > 1mo) Oral candidiasis (outside first 6-8 wks) Oral hairy leukoplakia Pulmonary tuberculosis, TB lymphadenitis Severe recurrent presumed bacterial pneumonia Acute necrotizing ulcerative gingivitis/periodontitis Lymphoid interstitial pneumonitis (LIP) Chronic lung disease incl bronchiectasis *Unexplained* anemia (<8g/dl), neutropenia (<500/mm3), or thrombocytopenia (<50,000/mm3) for >1 mo.
STAGE IV[b]	**WHO Presumptive Clinical Stage 4 (age < 18 mths)** For a symptomatic HIV-antibody positive infant age <18 mths, make a presumptive diagnosis of severe HIV disease (clinical stage 4) when*: a) Two or more of the following are present: • Oral candidiasis/thrush • Severe pneumonia • Severe Sepsis OR b) Diagnosis of any AIDS-indicator condition(s) can be made (see full stage 4 list below) *Other supporting evidence: recent HIV-related maternal death or advanced HIV disease in the mother; and/or CD4 <20% **WHO Stage 4 (all ages)** *Conditions which can be diagnosed using clinical signs or simple investigations:* o Unexplained severe wasting/stunting or severe malnutrition not

	adequately responding to standard therapy o Pneumocystis pneumonia o Recurrent severe presumed bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia) o Chronic Herpes simplex infection (of more 1 month duration) o Extrapulmonary tuberculosis o Oesophageal Candida o CNS Toxoplasmosis o HIV encephalopathy o Kaposi's sarcoma *Conditions where confirmatory diagnostic testing is necessary:* o CMV infection (CMV retinitis or infection of organ other than liver, spleen, or lymph nodes onset at age 1 month or more) o Extrapulmonary cryptococcosis (incl meningitis) o Any disseminated endemic mycosis (e.g. extra-pulmonary Histoplasmosis, Coccidiomycosis, Penicilliosis) o Cryptosporidiosis o Isosporiasis o Disseminated non-tuberculosis mycobacteria infection o Candida of trachea, bronchi or lungs o Acquired HIV related fistula o Non-Hodgkin's lymphoma o Progressive multifocal leucoencephalopathy o Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

a - Unexplained refers to where the condition is not explained by other causes.
b - Some additional specific conditions can also be included in regional classifications (such as reactivation of American trypanosomiasis [meningoencephalitis and/or myocarditis] in the WHO Region of the Americas, penicilliosis in Asia and HIV-associated rectovaginal fistula in Africa).

APPENDIX 5: WHO CLINICAL STAGING OF HIV FOR ADULTS AND ADOLESCENTS WITH CONFIRMED HIV INFECTION

STAGE I	Asymptomatic Persistent generalized lymphadenopathy (PGL)
STAGE II	*Unexplained* moderate weight loss (<10% of presumed or measured body weight) [a] Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media and pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrhoeic dermatitis Fungal nail infections
STAGE III	*Unexplained* [b] severe weight loss (>10% of presumed or measured body weight) *Unexplained* chronic diarrhea for longer than one month *Unexplained* persistent fever (above 37.5°C intermittent or constant, for longer than one month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections (eg, pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis *Unexplained* anaemia (<8.g/dl), neutropaenia (<0.5 x 10^9 per liter) and/or chronic thrombocytopaenia (<50 x 10^9 per liter)
STAGE IV[c]	HIV wasting syndrome Pneumocystis pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial,genital or anorectal of more than one month's duration or visceral at any site) Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Extrapulmonary tuberculosis Kaposi's sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Extrapulmonary cryptococcosis including meningitis Disseminated non-tuberculous mycobacterial infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis Chronic isosporiasis Disseminated mycosis (extrapulmonary histoplasmosis or coccidiomycosis) Recurrent septicaemia (including non-typhoidal *Salmonella*) Lymphoma (cerebral or B-cell non-Hodgkin) Invasive cervical carcinoma Atypical disseminated leishmaniasis Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

a - Assessment of body weight in pregnant woman needs to consider the expected weight gain of pregnancy.
b - Unexplained refers to where the condition is not explained by other causes.
c - Some additional specific conditions can also be included in regional classifications (such as reactivation of American trypanosomiasis [meningoencephalitis and/or myocarditis] in the WHO Region of the Americas and penicilliosis in Asia).