PREVALENCE OF HIV-RELATED OPPORTUNISTIC DISEASES AMONGST HAART PATIENTS AT THE FEDERAL MEDICAL CENTRE IN OWERRI, NIGERIA

A mini-thesis submitted in partial fulfillment of the requirements for the degree of Masters in Public Health at the School of Public Health,

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DECLARATION

I hereby declare that this work titled *"Prevalence of HIV-related opportunistic diseases amongst HAART patients at the Federal Medical Centre in Owerri, Nigeria"* is an original research carried out by me. It has not been submitted elsewhere for award of degree or fellowship. All the sources I used have been appropriately acknowledged and referenced.

Sign: 

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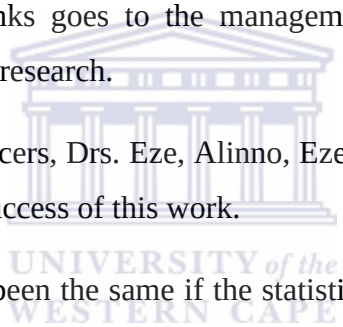

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LIST OF ABBREVIATIONS

AFB	Acid Fast Bacilli
AIDS	Acquired Immune Deficiency Syndrome
AOR	Adjusted Odds Ratio
ART	Anti-retroviral therapy
BMI	Body Mass Index
CD4	Cluster of Differentiation Antigen 4
CDC	Centers for Disease Control and Prevention
CMV	Cytomegalo Virus
CSF	Cerebrospinal Fluid
FHI	Family Health International
FMC	Federal Medical Centre
FMOH	Federal Ministry of Health
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
IQR	Interquartile Range
KS	Kaposi's Sarcoma

MAC	Mycobacterium Avium Complex
NPC	National Population Commission
OD	Opportunistic Disease
PCP	Pneumocystis Carinii Pneumonia
PLHIV	People Living with HIV
SD	Standard Deviation
SSA	Sub-Saharan Africa
STI	Sexually Transmitted Infection
TB	Tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States of America
UWC	University of the Western Cape
WHO	World Health Organization

DEFINITION OF TERMS

Anaemia: Haemoglobin concentration less than 10 g/dl (Sun *et al*., 2006)

Cluster of differentiation antigen 4 cell (CD4 cell): Antigen receptor component found mainly on T lymphocytes. In HIV infection, the CD4 cell count is continuously depleted and its value is a measure of the immune status of the individual (Fauci & Lane, 2005).

HAART: A combination of three antiretroviral drugs from at least two different drug classes (Sun *et al*., 2006; Lederberger *et al*., 1999).

Opportunistic disease: Unusual infections or malignancies that may be seen in individuals with compromised immune system such as in HIV/AIDS (Lederberger *et al*., 1999).

Overcrowding: Having more than two people who sleep in the same room.

ABSTRACT

Background: The hallmark of HIV infection is immunosuppression which predisposes to unusual infections and malignancies generally known as opportunistic diseases (ODs). Globally, ODs are the major cause of morbidity and mortality in people living with HIV (PLHIV). Since the advent of Highly Active Antiretroviral Therapy (HAART), a significant decline in AIDS progression and ODs has been observed globally. However, most of the evidence suggesting sustained decline in AIDS progression and ODs has come from high-income settings with relatively less burden of ODs in the pre-HAART era. The findings of studies in high-income settings may not be generalizable to resource-limited settings. Lack of information regarding the burden of ODs in HAART-experienced populations in Nigeria and the risk factors for their occurrence has made it difficult to fully assess the sustained efficacy of HAART in the country. The aim of this study was to investigate the prevalence of and risk factors for HIV-related opportunistic diseases amongst HAART patients at the Federal Medical Centre (FMC) in Owerri, Nigeria.

Study design and setting: A quantitative, cross-sectional descriptive and analytical study was conducted with 354 adult HIV-infected patients 15 years and above, who were on HAART for a minimum of 12 weeks at the HIV clinic of the FMC, Owerri, South-east Nigeria. Patients currently manifesting an OD whose onset ante-dated the commencement of HAART were excluded. The participants were recruited by simple random sampling.

Data collection: Using a structured questionnaire, data was collected by clinicians through interviews, physical and laboratory examinations for patients that provided informed consent and met the study criteria. The questionnaire captured patient's socio-demographic information and other relevant clinical/laboratory data.

Data Analysis: The data was analysed using Epi info version 3.5.1 and Open Epi Version 2.2.1. Descriptive statistics for HIV-related ODs were carried out using percentages and frequencies tables for categorical variables and means (SD) or medians (IQR) for numerical variables. In univariate analysis, the Chi-square test was used to determine significance of association between OD and socio-demographic and clinical variables while the Student "t"-test was used to compare group means. Logistic regression model (multivariate analysis) was used to determine the independent risk factors for the occurrence of ODs using parameters that had a p-value of

<0.25 on univariate analysis. All reported p-values <0.05 were considered statistically significant.

Results: The mean age of the participants was 41.1 ± 10.0 years; and females were in the majority (65.8%). Over 40% of them were rural dwellers, 50.4% belonged to the lower socio-economic class, and 55% had a monthly household income less than 20,000 Naira. Fifty percent (50%) of them had advanced immunosuppression at first presentation. The median duration of HAART (3 years) paralleled the median duration of HIV diagnosis (3.4 years) and HAART adherence rate was 78%. The overall prevalence of ODs was found to be 22.4%. Among the 76 patients diagnosed with ODs, the leading conditions were candidiasis (38.2%), TB (34.2%), dermatitis (25%), chronic diarrhoea (6.6%) and sepsis (6.6%). The independent risk factors for the occurrence of ODs were household income less than 20,000 Naira (Adjusted odds ratio [AOR] = 2.4, 95% CI 1.1-5.1), HIV duration of less than 3 years (AOR= 2.1, 95% CI 1.1- 4.2), advanced WHO clinical stage at baseline (AOR= 8.1, 95% CI 4.0-16.4), baseline haemoglobin less than 10 g/dl (AOR= 2.9, 95% CI 1.3-56.1), current CD4 cell count less than 200 cells/µl (AOR= 3.0, 95% CI 1.14-6.2), and HAART non-adherence (AOR= 5.4, 95% CI 2.6-11.2). Past history of TB was found to be a strong predictor of TB (AOR= 5.3, 95% CI 1.4-20.2).

Conclusions: Opportunistic diseases are common in patients receiving HAART in Nigeria and candidiasis and TB remain the leading conditions. Late presentation and HAART non-adherence are among the strongest risk factors for ODs in patients receiving HAART. Others include duration of HIV diagnosis less than 3 years, presence of anaemia at the time of first presentation and having a low CD4 cell count while on HAART. Beyond these clinical risk factors, poverty increases the risk of developing an OD during HAART and may emerge a strong determinant of HIV-related ODs in developing countries.

Recommendations: A high index of suspicion for ODs remains necessary in HAART patients. Health education on HIV screening and early presentation should be intensified. PLHIV who are anaemic before commencement of HAART, those with low CD4 cell count despite HAART use, and low-income earners should become target groups for a more aggressive evaluation for ODs. Prophylaxis for TB and fungal infections in the absence of active disease should be widely implemented in developing countries. HAART adherence should be intensified.

CHAPTER 1

INTRODUCTION

1.1 Background

With the history of HIV/AIDS in Nigeria spanning well over three decades, it is not surprising that the number of people living with HIV (PLHIV) has substantially increased over these years. It is currently estimated that 3.3 million people are living with HIV in Nigeria with a total of 220, 000 AIDS deaths in 2009 (UNAIDS, 2010). This currently places Nigeria as the country with the second largest number of PLHIV worldwide (FMOH, 2010). In response to the raging epidemic of HIV/AIDS, the Federal government of Nigeria in partnership with international collaborators established the national antiretroviral therapy (ART) programme in 2002 which led to increased access to HIV care and treatment (Odutolu, Ahonsi, Gboun & Jolayemi, 2006). The total number of PLHIV on ART steadily increased from 50,581 at the early stages of ART in Nigeria in 2005 to 302,973 in 2009 (FMOH, 2010). So far, the efforts are still sub-optimal as only one-third of patients requiring treatment in Nigeria have access to ART (FMOH, 2010).

The hallmark of HIV infection is immunosuppression which predisposes to unusual infections and malignancies which are generally known as opportunistic diseases (ODs) (Lederberger *et al.*, 1999). Globally, ODs are the major cause of morbidity and mortality in PLHIV (Sharma, Kadhiravan, Banga, Goyal, Bhatia & Saha, 2004; Komati *et al*, 2010). This is even more critical in sub-Saharan Africa (SSA) where the standard of living is generally poor and access to ART is still inadequate (UNAIDS, 2010). A striking feature of the reported clinical spectra of ODs in HIV/AIDS has been the contrasting findings from divergent socio-economic settings. In developed regions such as North America, Europe, and Australia, *Pneumocystis carinii* pneumonia (PCP), Kaposi's sarcoma (KS), oesophageal candidiasis, cytomegalovirus (CMV)-related disease and disseminated *Mycobacterium avium* complex (MAC) infection have each generally been reported in at least 20% of people with AIDS (Farizo, Bueliler & Chamberland, 1992; Jougla *et al.*, 1996; Dore, Li, McDonald & Kaldor, 2001). In developing regions such as SSA and Asia, where an estimated 90% of PLHIV reside, the predominant HIV-associated ODs include tuberculosis (TB), candidiasis, infective diarrhoea, meningitis, dermatitis and recurrent *Herpes simplex* infection (Hira, Dore & Sirisanthana, 1998; Holmes, Losina, Walensky,

Yazdanpanah & Freeberg, 2003). Some of the factors that may be contributing to this contrasting spectra of HIV-related ODs in developed and developing nations include socio-demographic, clinical and genetic factors as well as differences in HIV disease progression and infectious disease diagnostic capacity (Dore, Li, McDonald & Kaldor, 2001; De Beaudrap *et al.*, 2010).

Since the advent of Highly Active Anti Retroviral Therapy (HAART), a significant decline in AIDS progression and ODs has been observed in both developed and developing regions (Ledergerber *et al*., 1999; Ives, Gazzard & Easterbrook, 2001; Seyler, Messou, Gabillard, Inwoley, Alioum & Anglaret, 2007; Zhou, Paton & Ditangco, 2007). However, significant differences still exist in the burden of ODs in the era of HAART in these two regions. Most of the evidence suggesting the decline in AIDS progression and ODs has come from high-income settings with relatively less burden of ODs in the pre-HAART era, early and widespread access to ART and sophisticated diagnostic tools. The findings of studies in high-income settings may not be generalizable to resource-limited settings. For example, ODs remain a big challenge in HIV/AIDS patients receiving ART in SSA (De Beaudrap *et al*, 2010). In addition, there is insufficient knowledge about the factors that may be associated with the occurrence of ODs in HIV-infected populations receiving HAART in SSA.

1.2 Problem statement and study rationale

Opportunistic diseases constitute the major cause of morbidity and mortality in PLHIV even in the era of HAART (Sharma, Kadhiravan, Banga, Goyal, Bhatia & Saha, 2004; Komati *et al.*, 2010). This shortens the life expectancy of PLHIV. In addition, the high burden of ODs places additional economic strains on HIV care attributable to the additional cost of OD treatment. This is considered a significant burden for a developing nation like Nigeria.

Moreover, geographical differences exist in the spectrum of ODs. An evidence-based identification and detailed assessment of the prevalent ODs in PLHIV in the era of HAART in order to define local priorities in HIV care and inform targeted expenditure on OD prophylaxis and treatment is therefore needed.

In addition, timely intervention for ODs not only helps PLHIV to live longer, it also helps to prevent transmission of ODs such as TB to other people in the community (Saha *et al*., 2011).

Efforts to eliminate ODs in PLHIV cannot be successful if the risk factors for their occurrence are not well understood.

Since the current spectrum of ODs in ART-experienced populations in Nigeria as well as the predicting factors remain largely undetermined, it will be difficult to fully assess the impact and sustained efficacy of ART in the country. This study therefore sought to contribute to filling some of this gap by investigating the prevalence of ODs in HIV-infected Nigerian adults on HAART and also determined some of the socio-demographic and clinical risk factors associated with their occurrence.

1.3 Description of research setting

This study was carried out at the Federal Medical Centre (FMC), Owerri, Imo State, South-east Nigeria. This is a tertiary health institution that provides services to both urban and rural populations in Imo State and some other neighbouring towns in other States in South-east Nigeria especially Abia and Anambra States. Owerri is the capital of Imo State and is surrounded by other local government areas that are predominantly rural settlements. The predominant ethnic group is Igbo and is also the local language spoken. English language is officially spoken among literate groups in public and corporate private sectors. In Owerri town, people that belong to non-Igbo ethnic groups are very much in the minority and include major ethnic groups such as Hausa and Yoruba, as well as other minor ethnic groups such as Efik/Ibibio, Edo, and Ijaw. The major occupations of the people of Owerri are trading and civil service. Farming is also common especially on the outskirts of the town and in the surrounding rural settlements. Imo state has a population of 3.9 million (NPC, 2006). The prevalence of HIV in Imo State is 4.6% which is the same as the national HIV prevalence of 4.6% (FMOH, 2010).

The HIV clinic in FMC, Owerri which is otherwise called "*Heart-to-Heart Centre*" is a Family Health International (FHI)-facilitated HIV care and treatment centre that provides ambulatory services for about 5,000 patients out of whom approximately 2,000 adults (female to male ratio of 2:1) were receiving HAART as at September 2011 (Personal communication with the HIV clinic principal investigator, Dr Eugenia Ofondu, 5th September, 2011). The clinic has three sections: adult, paediatric, and prevention of maternal-to-child transmission sections. This study

was carried out in the adult clinic. In addition, FMC, Owerri has admission facilities for the treatment of ill HIV-infected patients requiring in-patient care under the care of specialist consultant physicians including an infectious diseases specialist, a dermato-venereologist, and a respiratory physician. The services of the HIV clinic include HIV counseling and testing, clinical supportive care of HAART-naïve patients, antiretroviral and OD drug treatment, and laboratory support services. HIV screening/confirmation, most laboratory investigations, ART, and cotrimoxazole prophylaxis, are provided free of charge.

The HIV clinic has a monitoring and evaluation section whose responsibilities include receiving notification from clinicians on patients with opportunistic diseases, reporting of adverse drug reactions, identification and tracking of treatment defaulters as well as identification of patients with treatment failure. Although these records are available both for patient management and research, most of the monitoring and evaluation activities focus on individual patients such that cohort monitoring is not routinely done at the centre.

1.4 Study aims and objectives

1.4.1 Aim

- To investigate the epidemiology of opportunistic diseases (ODs) in the era of HAART at the FMC in Owerri, Nigeria.

1.4.2 Specific objectives

- To estimate the prevalence of ODs in HIV-infected patients receiving HAART at FMC in Owerri, Nigeria.
- To describe the socio-demographic and clinical characteristics of patients on HAART experiencing ODs at FMC in Owerri, Nigeria.
- To determine independent risk factors for occurrence of ODs in patients on HAART at FMC in Owerri, Nigeria.

CHAPTER TWO

LITERATURE REVIEW

2.1 Global epidemiology of HIV/AIDS

Globally, 34 million people are estimated to live with HIV/AIDS and about 2 million people die annually from the disease with the most severe effects occurring in young adults in their economically productive years (UNAIDS, 2011). The majority of the new HIV infections (2.7 million) continue to occur in SSA (UNAIDS, 2011). Africa with just 10% of the world population is home to 70% of PLHIV worldwide (UNAIDS, 2011). The number of annual AIDS-related deaths worldwide is steadily decreasing from the peak of 2.1 million in 2004 to an estimated 1.8 million in 2010 (UNAIDS, 2011). The decline reflects the increased availability of ART, as well as care and support for PLHIV. However, the pattern of decline has significant regional variations (UNAIDS, 2011). In North America as well as Western and Central Europe, deaths due to AIDS began to decline soon after ART was introduced in early/mid 1990s while AIDS-related mortality only began to decline in SSA and the Caribbean in 2005 (UNAIDS, 2011). In Eastern Europe and Central Asia, the number of people dying from AIDS-related causes increased more than 10-fold between 2001 and 2010. In the same period, the number of people dying from AIDS-related causes increased by 60% in the Middle East and North Africa and more than doubled in East Asia (UNAIDS, 2011).

2.2 Natural history of HIV infection

Following HIV infection, there is usually a 2-4 week serologic and clinically silent period known as serologic latency or window period. Subsequently, a seroconversion or primary illness in the 6-8weeks following infection ensues, which may present with a flu-like illness. This often lasts for about three weeks and is usually associated with “recovery” (Fauci & Lane, 2005). At this stage, there is a drop in the CD4 cell count which reflects a compromise of the immune system. The primary infection is followed by a prolonged period of clinical latency during which the patient is often asymptomatic and the CD4 cell count is usually above 500 cells/µl (Fauci & Lane, 2005). As HIV infection progresses, the patient develops an array of symptoms and signs. During this period the CD4 cell count falls continuously and when it is below 200 cells/µl, the risk of developing ODs becomes high. AIDS represents the late clinical and immunological stage

of HIV disease. With advanced clinical disease death often ensues within a few months to years. The mean time to the development of AIDS is about 10 years in most reports (Fauci & Lane, 2005). However, there are some reports of a faster progression to AIDS in sub-Saharan Africa (Morgan & Whitworth, 2001).

2.3 Overview of progress in antiretroviral therapy

Although HIV was first discovered in the early 1980s (Fauci & Lane, 2005), ART was only introduced in Europe and North America in early/mid 1990s and progressively became available with easy access and sustained coverage within five years (UNAIDS/WHO, 2006). Although ART gradually trickled into low and middle-income countries in the late 1990s, established access to ART was only witnessed in early 2000 and access to ART has continued to be scaled up since then (UNAIDS/WHO, 2006). From a starting point of 400,000 people receiving ART in low and middle-income countries in December 2003, about 6.7 million people were receiving treatment by December 2010 (UNAIDS, 2011). However, this is still sub-optimal as the estimated ART coverage among adults and children in low- and middle-income countries is just about 47% (UNAIDS, 2010).

The Federal Government of Nigeria initiated the national ART programme in January 2002 as part of an expanded response to care and support for PLHIV. Under this programme, 10,000 adults and 5,000 children were treated with a 3-drug ART combination. At onset, the programme involved 25 treatment centres across the 6 geopolitical zones of the country and was subsidized at a cost of US$10 per month for each patient (Idigbe *et al.*, 2005). Unfortunately, in 2004 the programme suffered a major setback when it was hit by a shortage of drugs which lasted for about three months (Monjok, Smesny, Okokon, Mgbere, & Essien, 2010). During this time, many patients were off drugs or staggered their dosages for the three months, which led to a structurally-induced adherence problem. The programme subsequently resumed when US$ 3.8 million worth of drugs were delivered. Another programme was started in 2006 with the goal of providing drugs at no cost to about 250,000 HIV-positive patients. Nevertheless, Nigeria remains among the countries where HIV treatment coverage is far from desirable. At the end of 2009, only about one third of people with advanced HIV infection were on ART in Nigeria (FMOH, 2010).

2.4 HIV/AIDS and opportunistic diseases

Opportunistic diseases refer to unusual infections and malignancies which may develop in PLHIV in the course of their disease (Lederberger *et al.*, 1999). Overwhelming evidence indicates that the overall incidence of ODs in PLHIV increases with the degree of immunosuppression as reflected by the CD4 cell count (Yazdanpanah *et al.*, 2001, Salami, Olatunji & Oluboyo, 2006). The level of immunity of an individual can be assessed by determining the CD4 cell count which is an expression of the number of immune cells present. In healthy individuals with adequate immunity, the CD4 cell count is variable but ranges between 600 and 1,500 cells/µl. As shown in Fig. 2.1, the risk of specific HIV-related OD varies with the degree of immunosuppression (Crowe, Carlin, Stewart, Lucas & Hoy, 1991; Morgan & Whitworth, 2001). For example, infections with herpes viruses, candida, or pyogenic bacteria may occur in asymptomatic persons with moderate immunosuppression whereas the risk for PCP markedly increases when the CD4 count is less than 200 cells/µl (Masur *et al.*, 1989; Crowe, Carlin, Stewart, Lucas & Hoy, 1991). MAC infection, CMV disease and non-Hodkin's lymphoma typically develop when the CD4 cell count is less than 100 cells/µl (Masur *et al.*, 1989; Crowe, Carlin, Stewart, Lucas & Hoy, 1991). Other conditions such as TB and KS may be experienced at any level of CD4 cell count (Morgan & Whitworth, 2001; Nwuba, Okonkwo, Abolarin, Ogbu & Modebelu, 2012). A large percentage of PLHIV experience several ODs before death and their mortality is ultimately attributable to one of these events (Chan, Neaton, Saravolatz & Osterberger, 1995; Sharma, Kadhiravan, Banga, Goyal, Bhatia & Saha, 2004; Losina *et al*., 2006).

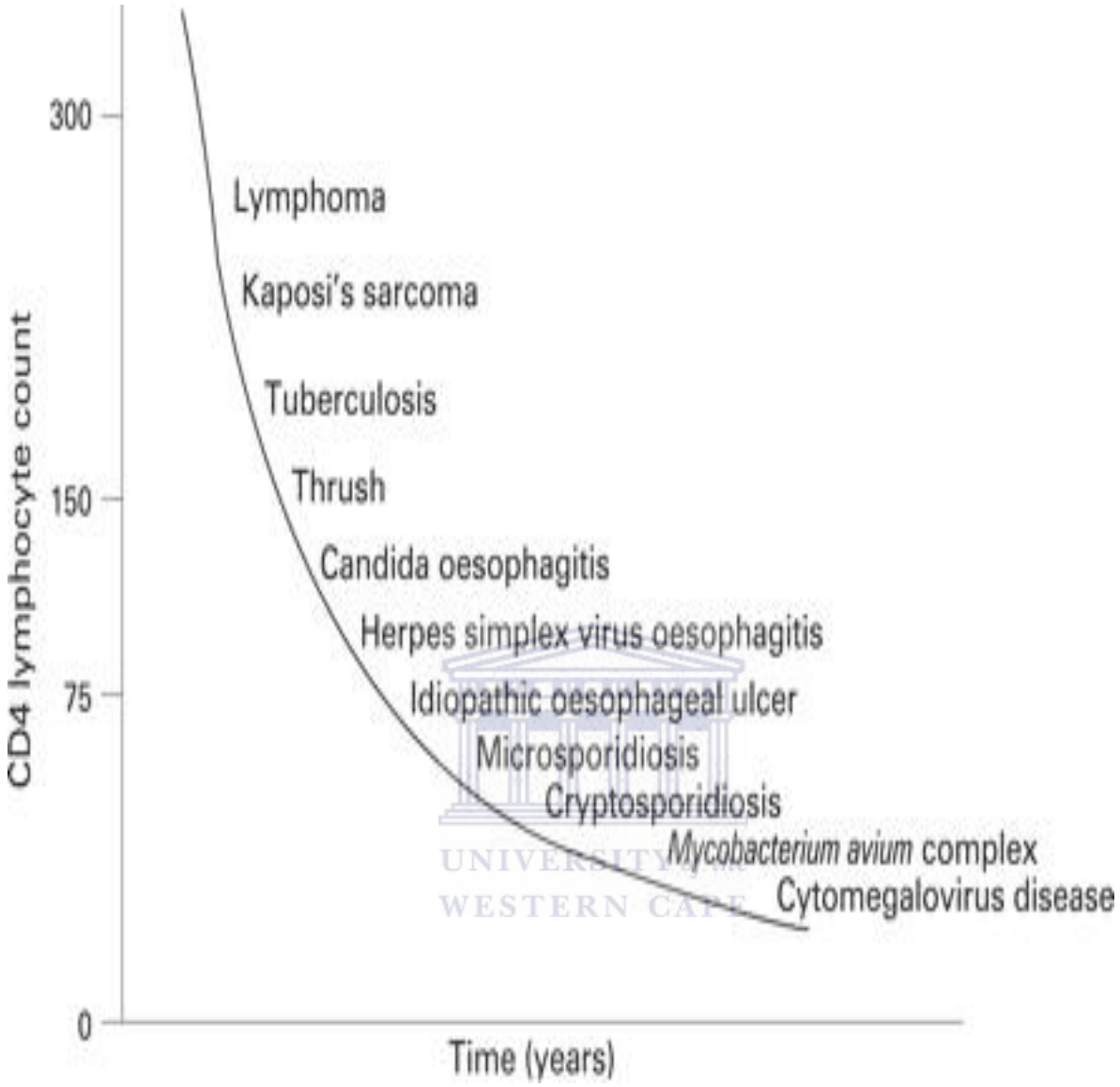

Fig 2.1: Relationship between specific HIV-related opportunistic diseases and CD4 cell count (Adapted from Wilcox & Saag, 2008)

A striking feature of the reported clinical profile of ODs in HIV/AIDS has been the contrasting findings from high and low-income countries. In a survey of 6,682 HIV-infected patients spanning 1990 to 1994 in the United States, 1,883 died from ODs during the follow up. The most common ODs experienced were PCP (45%), MAC infection (25%), HIV wasting syndrome (25%), bacterial pneumonia (24%), CMV disease (23%) and candidiasis (22%) (Chan, Neaton,

Saravolatz & Osterberger, 1995). It was observed that more diseases varied by geographical location than by demographic characteristics or risk behaviour of the patients. Similarly, in France, Jougla *et al.* (1996) found that the most frequently reported ODs in AIDS patients were toxoplasmosis (37%), CMV disease (37%), PCP (29%), KS (28%), HIV encephalopathy (27%), invasive candidiasis (23%), *Herpes simplex* virus infection (18%) and MAC infection (17%). Tuberculosis was relatively less common occurring in only 11% of the population. Unlike the report of Chan *et al.* (1995), the authors further observed that the diseases varied by HIV risk behaviour. Few differences in the pattern of ODs were observed by gender.

Contrary to the findings of studies in developed countries, TB tops the list of HIV-associated ODs in most low and middle-income countries of SSA and South-East Asia (Holmes, Losina, Walensky, Yazdanpanah & Freeberg, 2003; Singh, Bairy & Shivananda, 2003; Dhungel, Dhungel, Easow & Singh, 2008). In India, the commonly reported ODs were candidiasis (59%), TB (56%), and cryptosporidium diarrhoea (47%) (Singh, Bairy & Shivananda, 2003). *Pneumocystis carinii* pneumonia (7%), CMV disease (6%), *Herpes simplex* infection (3%) and toxoplasmosis (4%) were less common.

A more recent study in India in which 90% of the participants were not on ART made similar observations in the spectrum and rate of ODs (Ghate *et al.*, 2009). Tuberculosis was the most common OD with an incidence of 15.4 per 100 person-years, followed by oral candidiasis 11.3 per 100 person-years, and herpes zoster 10.1 per 100 person-years. Cryptococcal meningitis was far less common at 1.7 per 100 person-years. In their study, patients with CD4 cell counts of less than 200 cells/µl were six times more likely to develop ODs compared to those with CD4 cell counts more than 350 cells/µl ($p<0.001$).

Contrarily, TB, diarrhoea, and oesophageal candidiasis have been shown to have relatively lower prevalence rates in some HIV-infected patients in rural Thailand, another developing nation. Inverarity, Bradshaw, Wright and Grant (2002) observed that 32% of HIV-infected patients presenting for the first time between 1997 and 2000 in a mission hospital in rural Thailand had AIDS-defining ODs. The reported ODs included cryptococcal meningitis (15%), bacterial pneumonia (12%), extrapulmonary TB (12%), PCP (7%), cerebral toxoplasmosis (4%), pulmonary TB (3%), oesophageal candidiasis (2%), and sepsis (2%). However, the authors

opined that it is possible that TB and sepsis were under-diagnosed and further highlighted the need for improved diagnostic facilities and validation of clinical algorithms.

In a comprehensive review of HIV-related ODs in SSA using data from 18 countries [Nigeria not inclusive], the prevalence of common ODs were as follows: TB (27-61%), candidiasis (14-67%), parasitic chronic diarrhoea (6-42%), *Streptococcus pneumoniae* infections (25-31%), cryptococcal meningitis (0-50%), and PCP (1-11%) (Holmes, Losina, Walensky, Yazdanpanah & Freeberg, 2003). The authors acknowledged that the constraints of data on the burden of HIV-related OD in SSA include the lack of longitudinal studies with long follow-up periods, inability to estimate the time of seroconversion, and the variable OD diagnostic criteria occasioned by limited diagnostic facilities.

In a 2 year retrospective analysis of HIV-infected patients in Ilorin, North-central Nigeria, Salami, Olatunji and Oluboyo (2006) found that ODs occurred in 68.6% of the patients. Tuberculosis (pulmonary and extra-pulmonary), HIV encephalopathy, cryptococcal meningitis, KS and candidiasis (pulmonary) topped the list. It was also reported that the risk of death was four-fold higher in individuals with ODs. In another survey in North-central Nigeria, 56.7% of HIV-infected patients were found to present late in terms of stage of immunosuppression at first hospital visit. The commonest ODs among them were TB (61.8%), candidiasis (25%), septicaemia (21%), chronic diarrhea (18.4%), cryptococcal meningitis (9.2%), HIV encephalopathy (7.8%), and KS (7.8%) (Daniyam, Iroezindu, Shehu, Essien, Sati & Agaba, 2011). A multi-centre study in North-eastern Nigeria investigated ODs in HIV-infected populations and also found a high prevalence of 61.7% (Saidu, Bunza, Abubakar, Adamu, Ladan & Fana, 2009). Intestinal parasitic infections occurred in 28.5% of the participants, sexually transmitted infections (STI) in 22.1%, gastrointestinal candidiasis in 8.6% and TB in 6.7%. Despite the fact that these studies carried out in Nigeria are recent, none of them focused on HIV-related ODs in HAART patients. Although the overall prevalence of OD reported in these studies from Nigeria are similar, the relatively low burden of TB as an HIV-associated OD reported by Saidu *et al.* (2009) in North-eastern Nigeria is in sharp contrast with that documented in North-Central Nigeria by Salami *et al.* (2006) and Daniyam *et al.* (2011) where TB was the commonest HIV-associated OD. This difference may be due to a number of reasons. The studies by Salami *et al.* (2006) and Daniyam *et al.* (2011) were each carried out in one centre compared to that of Saidu *et al.* (2009) which was a multi-centre study with a sample size nearly double that of Salami *et al.* (2006)

and eight times larger than that of Daniyam *et al*. (2011). In addition, the differences in the age, immune status and TB exposure risks of their study populations could have also contributed.

There is paucity of data on the burden of some ODs such as PCP and MAC in Nigerian HIV-infected populations. While this may suggest their relative lower burden in the country, the fact that the appropriate diagnostic facilities for these conditions are generally lacking in the country should be borne in mind before drawing strong conclusions regarding them.

A possible argument at this point is to verify if environmental or genetic factors have any impact on the spectrum of HIV-related ODs. A review of the profile of ODs in people living in Australia was carried out to study the effect of country/region of origin (Dore, Li, McDonald & Kaldor, 2001). Tuberculosis prevalence was only 1% for both Australian and other industrialized country/region born AIDS patients. In contrast, TB prevalence was 10% in Asia-Pacific and 23% in SSA born AIDS patients. Prevalence of PCP was 27-34% and clearly the most commonly diagnosed condition in all country/region of birth categories except SSA. AIDS cases born in SSA had an increased risk of TB (OR=18.7; 95% CI= 9.2–38.2) and cryptococcosis (OR = 2.4; 95% CI= 1.1–5.4), but a decreased risk of oesophageal candidiasis (OR=0.3; 95% CI= 0.1–0.8) and PCP (OR=0.5; 95% CI= 0.3–0.9) compared to AIDS cases born in Australia. Tuberculosis risk was also elevated among AIDS cases born in Asia-Pacific (OR=9.6; 95% CI= 5.3–17.5) and other developing countries/regions (OR= 3.1; 95% CI= 0.9–10.4). The risk of AIDS-related ODs was similar for AIDS patients born in Australia and other industrialized country regions.

Del-Amo et al. (1996) also compared the spectrum of disease and severity of immune deficiency in HIV-infected African and non-African patients in London. HIV-infected African patients presented at lower levels of CD4 cell count and at a more advanced clinical stage of disease. Tuberculosis accounted for 27% of the initial episodes of AIDS-related OD in Africans but 5% in non-Africans while PCP was the initial AIDS-related condition in 34% of non-Africans but 17% for Africans.

While the studies by Dore *et al.* (2001) in Australia and Del-Amo *et al.* (1996) in London reviewed above made their observations based on racial disparities, another report by Yazdanpanah *et al.* (2001) highlighted in-country regional differences in the burden of HIV-related OD in France among people who did not have racial disparity. Their study population comprised HIV-infected persons from two different centres in Tourcoing and Aquitaine. They had similar populations including men who have sex with men (MSM), and injection drug users.

Their findings corroborated the widely-recognised observation that the incidence rates of the various ODs including PCP, CMV and toxoplasma encephalitis were significantly higher in participants with severe immunosuppression. In addition, they observed that the incidence of PCP (RR=1.9, 95% CI: 1.1-3.0) and CMV infection (RR=2.2, 95% CI: 1.4-3.4) were significantly higher in Tourcoing than in Aquitaine which was not attributable to differences in level of immunity between PLHIV in the two regions.

In summary, although the immunological stage of HIV infection is a strong predictor of the occurrence of ODs, it may not be out of place to suggest that the predominance of TB in PLHIV in SSA and Asia is still a reflection of the poverty-driven higher TB burden in the general population (Singh, 2002). This becomes a good justification to identify the clinical as well as the socio-demographic risk factors for the occurrence of ODs in a given HIV-infected population.

2.5 HAART and opportunistic diseases

Since the advent of HAART, a significant decline in AIDS progression and the incidence of ODs have been observed in both developed and developing regions (Ledergerber *et al*., 1999; Hung & Chang 2004; Sun *et al*., 2006; Seyler, Messou, Gabillard, Inwoley, Alioum & Anglaret, 2007; Zhou, Paton & Ditangco, 2007; Ives, Gazzard & Easterbrook, 2011). In fact, according to Kaplan *et al*. (2000), "the incidence of nearly all AIDS-defining opportunistic infections decreased significantly in the United States during 1992-1998"; an observation that was attributable to the introduction of HAART. Kaplan *et al.* (2000) further observed that the decline for specific ODs was even more impressive after longer duration of HAART in US cohorts. In their report, the incidence of PCP declined by 21.5% per year in 1996-1998 compared with 3.4% decline per year in 1992-1995 ($p<0.001$); MAC disease declined by 39.9% per year in 1996-1998 compared to 4.7% in 1992-1995 ($p<0.001$), while the incidence of oesophageal candidiasis declined by 16.7% per year in 1996-1998 compared to 0.2% in 1992-1995 ($p<0.001$). In another report from United States by Pallela *et al.* (1998), the incidence of any of the three major ODs (PCP, MAC disease, and CMV retinitis) declined from 21.9 per 100 person-years in 1994 to 3.7 per 100 person-years by mid-1997.

Such patterns of decline in AIDS-related ODs have also been reported in other cohorts in Canada, Western Europe, and Australia (Brodt, Kamps, Gute, Knupp, Staszewski & Helm, 1997;

Forest *et al.*, 1998; Barbiker *et al.*, 2002). In a multinational cohort study involving 6,941 PLHIV in Australia and ten European countries, when comparing the periods 1997-2001 and 1994-1996, there were significant HAART-induced decreases in various ODs including candidiasis from 17.0% to 5.7%; cryptosporidiosis from 3.1% to 0.2%; cytomegalovirosis from 5.9% to 0.6%; PCP from 17.0% to 4.4%; toxoplasmosis from 3.4% to 1.4% and TB from 6.4% to 2.6% (Barbiker *et al.*, 2002). Forest *et al.* (1998) in Canada, documented that the rate of decline in AIDS-related major ODs was highest for PCP, at 5 cases per 1,000 every 6 months from 1994 to 1996 (p=0.004). It was reported in Germany that the incidence of AIDS-related ODs had declined by more than 70% between 1992 and 1996 (Brodt, Kamps, Gute, Knupp, Staszewski & Helm, 1997).

In developing countries, most of the research assessing the impact of HAART on ODs lags behind studies in Western countries by about 5-10 years which is probably reflective of the time lag in accessibility and availability of HAART in the two socio-economic environments. Nevertheless, decline in the burden of ODs has also been observed in developing nations (Hung & Chang 2004, Sun *et al.*, 2006; De Beaudrap *et al.*, 2010). In a cohort of 1,044 Taiwanese patients accessing HAART over a 10 year period spanning 1994 to 2004, the rate of AIDS-related ODs dropped from 77.7% at enrolment (i.e. pre-HAART) to 56.3% three months after the introduction of HAART and further gently declined to 47.6% within 3-12 months of HAART (Sun *et al.*, 2006). The authors observed that the spectrum of ODs were similar in the three study periods (pre-HAART, early HAART era and later HAART era) with candidiasis, and TB being among the commonest conditions. In India, Srirangaraj and Venkatesha (2011), reported a drastic reduction of OD events from 68.5% to 8.3% after 6 months of HAART in a prospective observational cohort study of 108 HIV-infected patients accessing care over a one year period between 2006 and 2007. Interestingly, the pre-HAART and post-HAART spectra of ODs in the study of Srirangaraj and Venkatesha (2011) and that of Sun *et al.* (2006) were similar so cannot be the reason for the variable rates of OD decline reported between the two studies. While the study in India was carried out during a period in which access to ART in Asia was already well established, the report from Taiwan included people who were on treatment in the early years of ART and this may account for the differences in the rates of decline of HIV-related ODs attributable to HAART in the two Asian populations. Nevertheless, the fact that the report from

Taiwan had a sample size ten times larger than the Indian population and followed up their cohort for a much longer duration may readily explain the differences in the rates of OD decline observed.

In Brazil, South America, it has been demonstrated that HAART significantly reduced the rates of ODs, hospitalizations and mortality (Candiani, Pinto, Cardoso, Carvalho, Dias, Carneiro & Goulart, 2007). In that study, 371 HIV-infected Brazilian patients were observed from 1989 to 2003. The overall rate of ODs declined from 18.3 per 100 persons-years in the pre-HAART era to 2.6 per 100 persons-years in the post-HAART era. In multivariate analysis, the risk of developing an OD was 5.4 times greater before HAART.

The impact of HAART on AIDS-related ODs may not have been sufficiently explored in SSA partly because the majority of the HIV-infected populations requiring ART are yet to have access to it (UNAIDS, 2011). In Cote d'Ivoire, West Africa, Losina *et al*. (2007) demonstrated the independent effect of HAART in the reduction of severe ODs and death. The authors observed a CD4-independent reduction in risk of severe OD, death, or both for patients on HAART. This independent effect of HAART was found to be greater when patients were on HAART for more than 6 months. In Senegal, West Africa, De Beaudrap *et al.* (2010) documented that the incidence of AIDS-related ODs declined from 20.5 per 100 person-years during the first year of observation on HAART to 4.3 per 100 person-years during the fourth year but increased afterwards by 5% per month. The increase in the burden of ODs noticed after the fourth year of HAART makes the findings of this study peculiar compared to the others considering that studies that even followed PLHIV for longer durations of HAART in Western countries and Asia did not make such observations. This makes it imperative to investigate other HAART-related and non-HAART related factors that may compromise the long-term benefits of HAART in SSA where socio-cultural determinants of health play a strong role.

At this point, it is also useful to say that while prevalence and incidence studies can readily be used to investigate the burden of ODs in patients receiving HAART, one notable difference between the two approaches is that incidence studies make it possible to compare the burden of ODs at specified times in the study to the pre-HAART rates for the same population. This explains why De Beaudrap *et al.* (2010) were able to observe both periods of decline and increase in ODs in their cohorts.

Despite the well-documented efficacy of HAART in reducing the incidence of HIV-related ODs, the spectrum (relative frequencies) of common ODs have not changed significantly after introduction of HAART and neither has the burden of ODs changed by the same rates across various regions (Forest *et al.*, 1998; Ledergerber *et al*.; 1999; Sun *et al*., 2006; De Beaudrap *et al*., 2010). So far, most of the evidence suggesting progressive decline has come from high-income settings with relatively less burden of ODs in the pre-HAART era, early and widespread access to ART and sophisticated diagnostic tools (Ledergerber *et al*., 1999; Ives, Gazzard & Easterbrook, 2011). Opportunistic diseases exemplified by TB and candidiasis remain a big challenge in HIV/AIDS patients receiving HAART especially in SSA (De Beaudrap *et al*., 2010). For example, in 2,605 HIV-infected patients on HAART in South Africa followed up for 30 months, ODs manifested in 47.6% of the patients in whom mortality was recorded while on HAART (Mzileni, Mbenza & Chephe, 2008). Hence, it is of immense public health importance to further explore the burden of HIV-associated ODs and the associated risk factors in the era of HAART in SSA.

2.6 Risk factors for opportunistic diseases in patients receiving HAART

A number of studies have investigated the risk factors associated with the occurrence of ODs in patients receiving HAART. In the Swiss cohort study, Ledergerber *et al.* (1999) reported that the risk of developing an OD was highest during the initial months of HAART. Baseline CD4 cell count as well as subsequent CD4 cell counts and HIV viral load levels after commencement of HAART were strong predictors of the development of ODs. In the United States, decreasing CD4 cell count and increasing HIV viral load were the strongest predictors of the occurrence of ODs in adults and adolescents receiving HAART (Kaplan, Hanson, Jones & Dworkin, 2001). In several studies, longer duration of HAART has also been associated with lesser risk of ODs (Brodt, Kamps, Gute, Knupp, Staszewski & Helm, 1997; Hung & Chang 2004; Losina *et al*., 2007). This observation is however partly contradicted by De Beaudrap *et al*. (2010) who observed increased OD risk beyond four years of HAART after an initial decline before this time.

According to Manosuthi *et al*. (2007), the independent risk factors for developing ODs in adult Thai HIV-infected patients were baseline CD4 ≤50 cells/µl, male gender and low body weight.

In another Asian population, CD4 cell count during HAART was found not to be a significant predictor of ODs with the exception of TB and candidiasis (Srirangaraj & Venkatesha, 2011). The authors acknowledged that this was rather unusual and attributed this observation to the fact that all their patients were on cotrimoxazole prophylaxis which possibly prevented the occurrence of ODs in HAART-experienced patients who had low CD4 cell count.

In an evaluation of HIV-infected patients on HAART in South Africa, independent risk factors for TB were low CD4 cell count, high baseline viral load, low haemoglobin, low body mass index as well as male gender (Komati *et al*. 2010). In another study in South Africa, the occurrence of TB in patients receiving HAART was independently associated with baseline characteristics including CD4 cell count <100 cells/µl, WHO stage 3 or 4 disease and age less than 33 years (Lawn, Badri & Wood, 2005). Contrary to most available evidence, HIV viral load was not significantly associated with the risk of developing TB in this study. In addition, the risk of TB was not associated with a past history of TB, low socioeconomic status or gender (Lawn, Badri & Wood, 2005). The reasons for the disparity between the observations of Lawn *et al.* (2005) and those of Komati *et al.* (2010) may be partly related to time frame. While the population studied by Lawn *et al*. (2005) included PLHIV in the early stages of HAART when access to treatment was quite poor in SSA, Komati *et al*. (2010) focused on HAART-experienced PLHIV between 2004 and 2007.

So far, it may be appropriate to observe that only few studies such as those of Lawn, Badri and Wood (2005), Manosuthi *et al*. (2007), and Komati *et al*. (2010) considered the association between socio-demographic factors and development of ODs. Incidentally, these studies are all conducted in developing countries. The emphasis has virtually been on clinical parameters especially CD4 cell count and HIV viral load with little regard for socio-demographic factors. In SSA where socio-economic factors are far from desirable, ignoring their role in critical health issues such as ODs in HIV-infected patients on HAART will be a fundamental oversight.

CHAPTER THREE

METHODOLOGY

3.1 Study design

This was a *quantitative, cross-sectional descriptive and analytical study.* It involved the description of the prevalence of opportunistic diseases (ODs) in HIV-infected patients receiving HAART in Owerri, Nigeria. Analysis of the risk factors for the occurrence of the ODs was also carried out.

The possibility of a cohort study in order to assess incidence of ODs rather than prevalence was considered for this study but some of the anticipated drawbacks made an alternative study design difficult. For example, a retrospective analysis using already existing records on ODs would have been less capital-intensive. However, it may limit the strength of some of the findings considering that the privilege of employing a rigorous process in arriving at definitive OD diagnosis will be lost. On the other hand, embarking on a prospective cohort study was not considered feasible in view of the limited time and resources available for the mini-thesis.

3.2 Study population

The study population comprised of adult HIV-infected patients 15 years and above who were on HAART at the HIV clinic of the FMC, Owerri, South-east Nigeria. Patients included in the study were those whose HIV positive status was confirmed by Western blot, and they consented to the study. In addition, they were required to have received HAART for a minimum of 12 weeks. This was to ascertain that they had received HAART long enough to have achieved virological suppression and immune reconstitution. HAART-naïve patients and those currently manifesting an OD whose onset ante-dated the commencement of HAART were excluded from the study.

3.3 Sample size

The sample size was calculated using the formula for prevalence studies proposed by Krejcie & Morgan (1970):

$$n = \frac{\chi^2 \times N \times P \times (1 - P)}{[ME^2 \times (N - 1)] + [\chi^2 \times P \times (1 - P)]}$$

Where:

n= minimum sample size

χ^2 = the table value of Chi-square at 1 degree of freedom for 95% confidence interval = 3.84

N= population size i.e. total number of adult patients on HAART at FMC, Owerri= 2,000

P = prevalence of ODs in a previous study in South Africa = 47.6% (0.467)
(Mzileni, Mbenza & Chephe, 2008)

ME = Desired margin of error (i.e. level of precision) = 5% (0.05)

This formula estimated a minimum sample size of 322 patients at a 95% confidence interval and 5% precision based on prevalence of ODs of 47.6% in the mortality data of HIV-infected patients on HAART in a previous study in South Africa (Mzileni, Mbenza & Chephe, 2008) using a population of approximately 2,000 HIV-infected adults currently on HAART at the study site (FMC, Owerri HIV clinic data office records). The study in South Africa was used due to lack of such data from Nigeria and neighbouring countries. However, to accommodate events such as poorly completed questionnaires and incomplete results, additional 10% of the minimum sample size was enrolled which increased the sample size to 354.

To further verify the sample size calculation, a sample size table which employed this formula with various levels of precision, population size and the related sample size is shown in appendix 9 (The Research Advisors, 2006).

3.4 Sampling procedure

After applying the exclusion criteria, a systematic sampling method with a random starting point was used to recruit 354 patients from a population of 1,560 HIV-infected patients on HAART who were scheduled to visit the clinic within the 3 months of data collection. A sample interval of 3 was used such that every third person was selected. A random starting point between 1 and 3 was selected and subsequently every third person was selected until the required sample size of 354 was attained.

3.5 Opportunistic disease diagnostic criteria

The diagnosis of opportunistic diseases was made according to standard guidelines where possible and facilities available. Where diagnosis was entirely based on clinical grounds, two independent physicians involved in HIV care and management were required to have the same assessment before such diagnosis was accepted.

Candidiasis was detected by clinical examination followed by isolation of the yeasts from oropharyngeal or vaginal swabs.

Tuberculosis screening was offered to the patients based on a TB screening algorithm for HIV-infected patients (Cain *et al.*, 2010). Tuberculosis diagnostic algorithm was subsequently used to evaluate patients with a positive TB screening response (i.e. patients who reported having at least one of the 3 screening symptoms of cough of any duration, fever of any duration or night sweats of ≥3 weeks in the preceding 4 weeks).

Pulmonary TB was defined as presence of cough with or without fever, weight loss, night sweats or haemoptysis and demonstration of acid fast bacilli (AFB) in two or more sputum samples and/or chest X-ray features compatible with TB (Sharma, Kadhirava, Banga, Goyal, Bhatia & Saha, 2004; Ghate *et al*., 2009).

Extra-pulmonary TB was diagnosed as clinical evidence suggestive of TB without features of pulmonary involvement followed by histology of lymph node biopsy [for *TB lymphadenitis*], or followed by findings of exudative pleural effusion accompanied by clinical response to anti-tuberculous drugs [for *pleural TB*], or followed by ultrasonography of the abdomen for evidence of lymph nodes accompanied by clinical response to anti-tuberculous drugs [for *abdominal TB*] (Ghate *et al*., 2009; Sharma, Kadhirava, Banga, Goyal, Bhatia & Saha, 2004).

Disseminated TB was defined as clinical features suggestive of TB with concurrent involvement of at least two non-contiguous organs, with positive sputum smear and/or histopathological and/or radiological evidence of TB (Sharma, Kadhirava, Banga, Goyal, Bhatia & Saha, 2004).

For patients with negative sputum AFB despite strongly suggestive clinical and/or radiological features and patients whose diagnosis of extrapulmonary TB was not based on definitive tests such as histology, further supportive laboratory evidence especially elevated erythrocyte sedimentation rate (ESR), followed by clinical response to anti-tuberculous drugs at least in the intensive phase of treatment was further required before diagnosis of TB was accepted. For any

patient in this category whose anti-tuberculous drug response was not ascertained, the diagnosis of TB was not upheld.

Cryptococcal meningitis was diagnosed based on clinical evidence of meningitis with demonstration of cryptococcal yeast cells in the cerebrospinal fluid by Indian ink staining.

Chronic diarrhoea was initially diagnosed based on history and the responsible aetiologic agent was then isolated by appropriate stool analysis.

Sepsis was defined as the presence of ≥2 of the following: body temperature >38°C or <36°C; pulse rate >90 beats/min, respiratory rate >20 breaths/min, white cell count >12 X 10^9/l or <4 X 10^9/l or >10% immature (band) forms, in the presence of infection (Russell, 2006). The responsible aetiologic organism for the sepsis was subsequently identified by blood culture.

Bacterial pneumonia was diagnosed as clinical evidence of pneumonia with supportive chest X-ray infiltrates and positive sputum bacteriological test.

Kaposi's sarcoma was confirmed by histology of tissue biopsy obtained from the skin lesion following clinical evaluation.

Herpes zoster was diagnosed based on clinical evidence of prototypic painful skin eruptions with characteristic dermatomal distribution.

Genital herpes was diagnosed based on clinical evidence of painful genital ulcer preceded by vesicles with negative veneral disease research laboratory (VDRL) test for syphilis.

Genital wart was diagnosed based on the characteristic lesion on clinical examination.

3.6 Other case definitions

3.6.1 Socio-economic classification

The socio-economic class of the family was assessed using the father's occupation/income and the maternal educational attainment as recommended for Nigeria by Olusanya, Okpere & Ezimokhai (1985). This method stratifies socio-economic class into five classes I to V. Class I represent the upper cadre, classes II and III the middle cadre while classes IV and V are the lower cadre. The father's occupation had a cumulative score of 3 while the mothers' educational attainment had a cumulative score of 2. The total score from both parameters placed each participant in the respective classes. The scoring system is described below:

Father's occupation:

Score 1– professionals, top civil servants, politicians, high level businessmen.

Score 2– middle level bureaucrats, skilled artisans and well to do traders.

Score 3– unskilled workers and those whose income is at or below the national minimum wage.

Mother's educational attainment:

Score 0 – tertiary education – university, polytechnic (higher national diploma).

Score 1- secondary education– secondary school, college of education, ordinary diploma

Score 2– primary education or no schooling.

This classification system is judged relevant in developing countries like Nigeria where most mothers are uneducated considering that mother's education has been shown to be positively associated with health care knowledge and heath seeking behaviour in the family irrespective of household income (Otta, 1992; Alaka & Stephenson, 2005).

3.6.2 CD4 cell count classification and WHO clinical staging

The CD4 cell count of the participants were categorised into three groups using the Centers for Disease Control and Prevention classification as follows: ≥500 cells/µl, 200-499 cells/µl, and <200 cells/µl (CDC, 1993).

The WHO clinical staging system for adults (WHO, 2005) sorts patients into one of four hierarchical clinical stages ranging from stage 1 (asymptomatic) to stage 4 (AIDS). At the point of entry into the HIV care programme of the clinic, each patient was assigned to a particular stage if they demonstrated at least one clinical condition in that stage's criteria. Because patients remain at a higher WHO stage after they recover from the clinical condition which placed them in that stage, they are not re-staged in the course of management (Malamba, Morgan, Clayton, Mayanja, Okongo & Whitworth, 1999). The details of the WHO clinical staging system is shown in Appendix 7.

3.6.3 Drug adherence

Adherence to HAART was assessed using both tablet counting and self-reporting methods. In the tablet counting method, pharmacy medication records for patients were matched by the pharmacist against the not-yet-used medicines brought to the pharmacy by the patients as a routine for refill of prescriptions and the number of doses that ought to have been taken that were

missed were recorded (Era & Arute, 2008). Patient's self-reporting method was carried out as previously described by Weiser *et al*. (2003). In this method, patients were interviewed about their adherence over the previous day, previous week and previous month successively in an attempt to minimize recall bias. In both methods, adherence was defined as taking 95% of prescribed doses over the previous month which corresponded to missing no more than one dose in a 10-day period [in a 2 times a day dosing regimen], one dose per week [in a 3 times a day regimen] or one dose per month [in a once daily regimen] (Era & Arute, 2008). Patients were therefore said to have HAART non-adherence if they missed more than 5% of their doses. Where there was discrepancy between the rates obtained by the two methods, adherence rate obtained in the counting method was used. Cotrimoxazole adherence was determined in the same manner as stated above for HAART adherence.

3.7 Data collection

A *structured questionnaire* (Appendix 6) was used as the data collection tool. The questionnaires were administered to the patients by 3 clinical staff at the adult ARV clinic supervised by the researcher. The information contained in the questionnaire was based on parameters judged to be relevant to the study from the available literature. The information was separated into 3 sections. Section A was for the socio-demographic data. Section B contained the relevant medical history and physical examination findings while Section C captured the laboratory investigation results such as CD4 cell count, sputum AFB, chest x-ray, stool microscopy, cerebrospinal fluid (CSF) analysis, blood, sputum and urine cultures as well as tissue histology where appropriate. For patients who required further laboratory investigation for the diagnosis of HIV-related OD, samples were collected on the spot (as already explained to them before they consented) and the laboratory results were entered as soon as they were available. Some clinically-relevant instruments that were used in the study included s*tadiometer* for height measurement, w*eighing scale, mercury clinical thermometer and a digital camera*. The digital camera was used to obtain pictures of externally-visible diagnoses such as oral candidiasis, dermatitis, and Kaposi's sarcoma after obtaining informed consent. Patients' were assured that their facial identity will be concealed when the pictures will be displayed. Data collection involving contact with the patients spanned a period of 11 weeks.

3.8 Sample collection, storage and laboratory analysis

Depending on the clinical presentation of the patient, relevant specimens were collected such as sputum, oropharyngeal swab, high vaginal swab, stool, blood, urine, CSF. Microbiology samples for culture collected early in the day (8:00-12:00) were inoculated and subsequently incubated within official working hours (before 16:00) while those collected later in the day (14:00-16.00) were preserved in –80 ºC freezer for analysis the following morning. All samples were appropriately labeled and handled according to standard biosafety regulations. With the exception of histology, sample storage and analysis was carried out at the FHI-facilitated laboratory at the FMC Owerri. This is a modern laboratory with dedicated standby generator which ensures constant electricity supply for adequate preservation of samples in a –80 ºC freezer.

For TB, three sputa specimen were collected – spot sample at first contact with the patient, early morning sample the following day and another spot sample at the time of submission of the early morning sample. All three samples were used to make separate smears and stained by Ziehl-Neelsen method for AFB. Sputum AFB samples were routinely collected and analysed in the morning hours as part of the TB laboratory protocol so did not require storage. Direct saline and iodine mounts were prepared for stool samples and examined under the microscope for ova, larvae, trophozoites or cysts of intestinal parasites. For coccidian parasites such as cryptosporidium, stool specimens were examined by modified Ziehl-Neelsen technique. For candidiasis, oropharyngeal or vaginal swab specimens were cultured on to Sabouraud's dextrose agar and the fungal colonies were subsequently identified by the germ tube test. Cerebrospinal fluid preliminary microscopy and chemistry samples were routinely analysed on an emergency basis so did not require storage. In the CSF samples, cryptococcus was examined for by Indian ink wet mount. Bacteriological identification of organisms in the sputum for bacterial pneumonia employed both Gram staining techniques and culture in appropriate media. Aerobic and anaerobic blood cultures were carried out using appropriate media.

Venous blood samples for CD4 cell quantification were collected in the mornings and analysed within 2-3 hours using flow cytometry as obtainable in the laboratory protocol due to instability of CD4 cells *in vitro*. The haematology samples were analysed on the day of collection using haematology autoanalyser while blood chemistry samples were collected in appropriate sample

bottles and stored in a –80 ºC freezer for analysis within 24-48 hours using a blood chemistry autoanalyser. Biopsy samples collected following clinical diagnosis of Kaposi's sarcoma or TB lymphadenitis were preserved in formalin and moved to the histopathology laboratory of the hospital for histology.

3.9 Validity, reliability and generalizability

In order to ensure validity, a systematic sampling technique with a random starting point was adopted to minimize bias and to give every participant an equal chance of being selected. In addition, to eliminate confounding from HIV-related ODs ante-dating the commencement of HAART, only patients who had received HAART for a minimum of 12 weeks were selected. The 12 week period was to ensure that such patients had received HAART long enough to have achieved virological suppression and immunogical recovery. As much as possible OD diagnosis was based on standard definitions. Logistic regression analysis was used to control for potential confounders for OD risk factors.

To ensure reliability, a pilot testing of the questionnaire was carried out and pertinent minor modifications made. Also, before a clinical diagnosis of an OD was accepted, at least 2 physicians involved in HIV care and management were required to agree on the diagnosis and this was subsequently confirmed by laboratory investigations where relevant and possible. Due to difficulties in TB diagnosis in PLHIV, relevant TB screening and diagnostic algorithms were employed and where smear positivity or histologic diagnosis was not possible, additional supportive laboratory evidence and clinical response to treatment were employed to strengthen TB diagnosis. With the exception of histology, all the laboratory investigations were carried out in the same laboratory (FHI-sponsored laboratory, FMC, Owerri) using the same protocol for specific investigations with standard quality assurance guidelines. At least two trained laboratory scientists were required to agree on each laboratory diagnosis before it was accepted. Data analysis was carried out independently by the statistician and the researcher and the findings compared for conformity.

To improve generalizability, the study participants were selected from a general population of HIV-infected patients on HAART at the clinic. In addition, a random sampling technique was used to ensure that each individual had an equal chance of being selected.

3.10 Ethical considerations

Ethical clearance for the study was obtained from the Higher Degree Committee of the University of the Western Cape (UWC), South Africa (Appendix 1) and the Ethics Committee of Federal Medical Centre, Owerri, Nigeria (Appendix 2). An informed consent form (Appendix 3/4) was signed or thumb-printed by each patient before recruitment. Prior to this, the study and what it entailed was fully explained to the participants (Appendix 5). All information obtained from the patients as well as their laboratory investigation results were handled with confidentiality. Individuals diagnosed to have any OD were referred for appropriate treatment. The patients were not asked to pay any money for any part of the study. They were made to understand that participation in the study was voluntary and that they were at liberty to withdraw from the study at any stage without prejudice to their future management.

3.11 Data analysis

3.11.1. Data handling and cleaning

During data collection, questionnaires were constantly checked for errors. Data entry and analysis were carried out using the Epi Info version 3.5.1 statistical software (CDC, Atlanta, Georgia, 2008) and Open Epi Version 2.2.1. Two separate Epi Info views were created, one by the researcher and another by a statistician. Data entries from the questionnaires were then carried out using designated codes independently in the two Epi Info views. At the end of data entry, all the variables in the two views were listed and the data sets were compared for discrepancies and incomplete entries. Observed discrepancies were investigated by recourse to the specific questionnaire(s) affected and the corrections were effected. For discrepancies or errors which could not be corrected by reference to the questionnaire(s), the hospital folders or laboratory result data base were contacted for verification. Any issues which remained unresolved were subsequently classified as incomplete data. Out of the 354 questionnaires administered, 15 were classified as having incomplete data so only 339 were included in the final data analysis.

3.11.2 Descriptive and analytical statistics

For descriptive statistics, frequency tables of categorical variables were made both for socio-demographic variables (such as gender, occupation, socio-economic class, ethnicity, and residence) and clinical parameters (such as OD presence, HAART adherence, cotrimoxazole prophylaxis, and WHO clinical stage). Prevalence of HIV-related ODs was described as a simple proportion in percentage first as an aggregate variable and then for the individual ODs. Measures of central tendency (mean and median) and dispersion (standard deviation, SD; interquartile range, IQR) were used to describe numeric variables. Mean (SD) was used for normally distributed variables such as age, BMI, haemoglobin while median (IQR) was used to describe non-normally distributed parameters such as CD4 cell count, duration of HIV diagnosis, and duration of HAART.

In terms of univariate analytical statistics, the Chi-square test was used to determine significance of association between OD and various socio-demographic and clinical variables. When the expected cell values were less than 5, Fisher's exact test was used. The Student "t"-test was used to compare group means or median values. For multivariate analysis, backward stepwise logistic regression was used to determine the independent socio-demographic and clinical risk factors for the occurrence of ODs (as an aggregate variable) using parameters that had a p-value of <0.25 on univariate analysis. However, parameters which *a priori* were known risk factors for OD which had p-value >0.25 were also included in the logistic model. All reported p-values <0.05 were considered statistically significant.

CHAPTER FOUR

RESULTS

4.1: Socio-demographic characteristics of the study participants

Out of the 354 patients that consented to the study and had questionnaires administered on them, 339 had complete responses and laboratory results. The socio-demographic characteristics of the study participants are shown in Table 4.1. The participants were between 18 and 68 years with a mean age of 41.1 ± 10.0 years. The highest number of participants was between 31-40 years (36.0%). Female subjects were in the majority (65.8%). As shown in Fig. 4.1, men were significantly older with a mean age of 46.8 ± 9.2 years compared to 38.1 ± 9.2 years in women, $p<0.0001$.

Most of the participants were either married (59.3%) or widowed (20.6%). The majority (73.1%) of them had at least secondary level of education. The predominant occupations were trading (41%), civil service (19.8%) and farming (8.3%). Thirty four (10.0%) were unemployed. They were largely of Igbo ethnicity (93.2%); the remaining participants belonged to other ethnic groups including Efik/Ibibio- 9 (2.7%), Hausa/Fulani- 7 (2.1%), Tiv-5 (1.5%), and Yoruba- 2 (0.6%). Urban dwellers had a slight majority (56.3%). One hundred and eighty six (54.9%) patients had a household income of less than 20,000 Naira per month (<133 US dollars per month). The predominant household size was 5-8 persons per household reported in 158 (47.6%) of the participants. The number of rooms in the apartment where the participants resided ranged from 1 to 4 with a fairly equal distribution. Ninety eight (28.9%) reported having more than two people inclusive of themselves in a room. Half of the respondents (50.4%) were in the lower socio-economic class while only 27 (8.0%) were in the upper class.

Table 4.1: Socio-demographic characteristics of the study participants

Characteristic	N=339 n (%)
Gender	
Female	223 (65.8)
Male	116 (34.2)
Age (years)	
≤ 30	51 (15.0)
31-40	122 (36.0)
41-50	106 (31.3)
51-60	41 (12.1)
>60	19 (5.6)
Marital status	
Married	201 (59.3)
Single	46 (13.6)
Separated/divorced	22 (6.5)
Widowed	70 (20.6)
Occupation	
Trader	139 (41.0)
Civil servant	67 (19.8)
Farmer	28 (8.3)
Technician	13 (3.8)
Student	20 (5.9)
Others	38 (11.2)
Unemployed	34 (10.0)
Educational status	
None	7 (2.1)
Primary	84 (24.8)
Secondary	158 (46.6)
Tertiary	90 (26.5)
Household income (Naira, =N=)	
<20,000	186 (54.9)
20-50,000	73 (21.5)

51-100,000	50 (14.7)
>100,000	30 (8.8)
Household size/No of dependents	
≤4	114 (34.3)
5-8	158 (47.6)
>8	60 (18.1)
Rooms in apartment	
1	80 (23.6)
2	99 (29.2)
3	69 (20.4)
4	91 (26.8)
People per room	
≤2	241 (71.1)
>2	98 (28.9)
Socio-economic class	
Upper (class I)	27 (8.0)
Middle (class II & III)	141 (41.6)
Lower (class IV & V)	171 (50.4)
Ethnicity	
Igbo	316 (93.2)
Others	23 (6.8)
Residence	
Urban	191 (56.3)
Rural	148 (43.7)

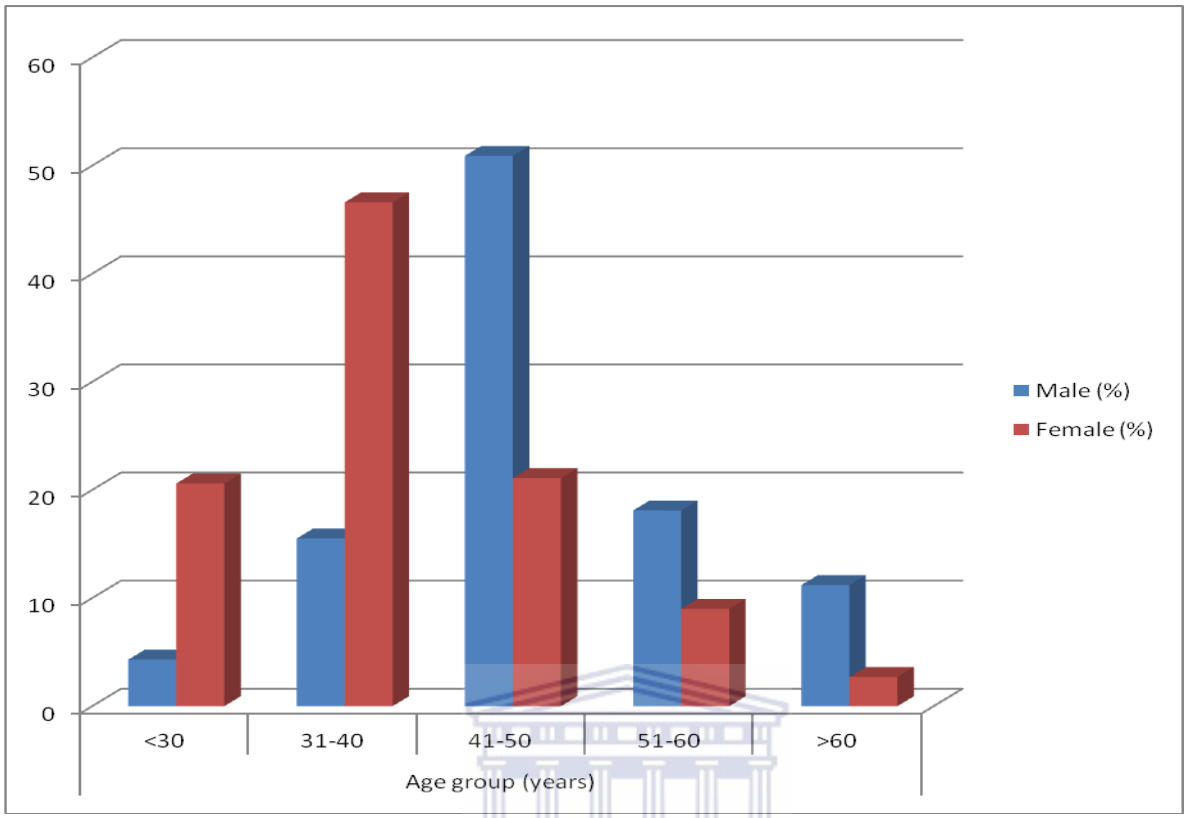

Fig. 4.1: Age distribution of the participants by gender

4.2 Clinical characteristics of the study participants

The clinical characteristics of the study participants are shown in Table 4.2. The duration of HIV diagnosis among the study participants ranged from 6 months to 10 years with a median (IQR) of 3.4 (2.0-6.0) years. There was no difference between men and women in terms of duration of HIV diagnosis; 3.5 (2.0-6.0) and 3.3 (2.0-5.6) years respectively (p=0.77). The duration of HAART ranged from 4 months to 118 months (9.8 years) with a median of 35 (20-50) months. There was also no difference between men and women in the median duration of HAART, 36 (22-54) months and 34 (20-48) months respectively (p=0.11). The majority (77.6%) were adherent on HAART. Two hundred and ninety seven (87.6%) participants were receiving cotrimoxazole prophylaxis with an adherence rate of 75.1%.

At baseline (i.e. at entry point pre-HAART), most of the participants belonged to either WHO clinical stage 1 (41%) or stage 2 (31.3%). The median baseline CD4 cell count of the patients was 200 (110-263) cells/µl and only 12 (3.5%) had baseline CD4 cell count ≥500 cells/µl. Their mean baseline haemoglobin was 11.2 ± 2.0 g/dl and 76 (22.4%) had anaemia at baseline. The median current CD4 cell count of the patients was 357 (211-496) cells/µl and 84 (24.8%) had CD4 cell count ≥500 cells/µl. Their mean current haemoglobin was 11.6 ± 1.8 g/dl and only 36 (10.6%) had anaemia. The mean current BMI of the participants was 24.5 ± 5.5 kg/m^2 and 51 (15.0%) were underweight. Seventy three (21.2%) had a past history of TB treatment, 52 (15.3%) had hypertension, and 11 (3.2%) had diabetes mellitus. Positive history of on-going alcohol consumption was recorded in 72 (21.2%) participants while 24 (7.1%) were current smokers.

Table 4.2: Clinical characteristics of the study participants

Characteristics	N=339
Duration of HIV diagnosis (years), median (IQR)	3.4 (2.0-6.0)
Duration of HAART (months), median (IQR)	35.0 (20.0-50.0)
HAART adherence,† n (%)	263 (77.6)
Cotrimoxazole prophylaxis, n (%)	297 (87.6)
Cotrimoxazole adherence (N=297), n (%)	223 (75.1)
Baseline WHO clinical stage	
1	139 (41.0)
2	106 (31.3)
3	76 (22.4)
4	18 (5.3)
Baseline CD4 cell count (cells/µl)	
<200	168 (49.6)
200-499	159 (46.9)
≥ 500	12 (3.5)
Current CD4 cell count (cells/µl)	
<200	75 (22.1)
200-499	180 (53.1)
≥500	84 (24.8)
Baseline haemoglobin (g/dl), mean ± SD	11.2 ± 2.0
Current haemoglobin (g/dl), mean ± SD	11.6 ± 1.8
BMI (current) [Kg/m^2], mean ± SD	24.5 ± 5.4
Past history of TB treatment	73 (23.7)
Hypertension	52 (15.3)
Diabetes mellitus	11 (3.2)
Alcohol consumption	72 (21.2)
Cigarette smoking	24 (7.1)

BMI= body mass index; HAART= highly active antiretroviral therapy; HIV=human immunodeficiency virus; IQR=interquartile range; TB=tuberculosis; SD=standard deviation; WHO=world health organisation

†Adherence refers to the proportion of patients with drug adherence level of >95%. The reported adherence was based on both self-reported and tablet counting methods.

4.3 Prevalence of opportunistic diseases

Out of 339 participants, 76 had diagnosed opportunistic disease(s) giving an overall prevalence of 22.4% (95% C.I 18.2-27.3%) (Fig. 4.2). The overall prevalence of OD was similar in men, 24 (20.7%) and women, 52 (23.3%). The highest overall prevalence of OD was recorded in those between 31 and 40 years (35.5%), closely followed by the 41-50 years (30.3%), and ≤30 years (27.6%) age groups.

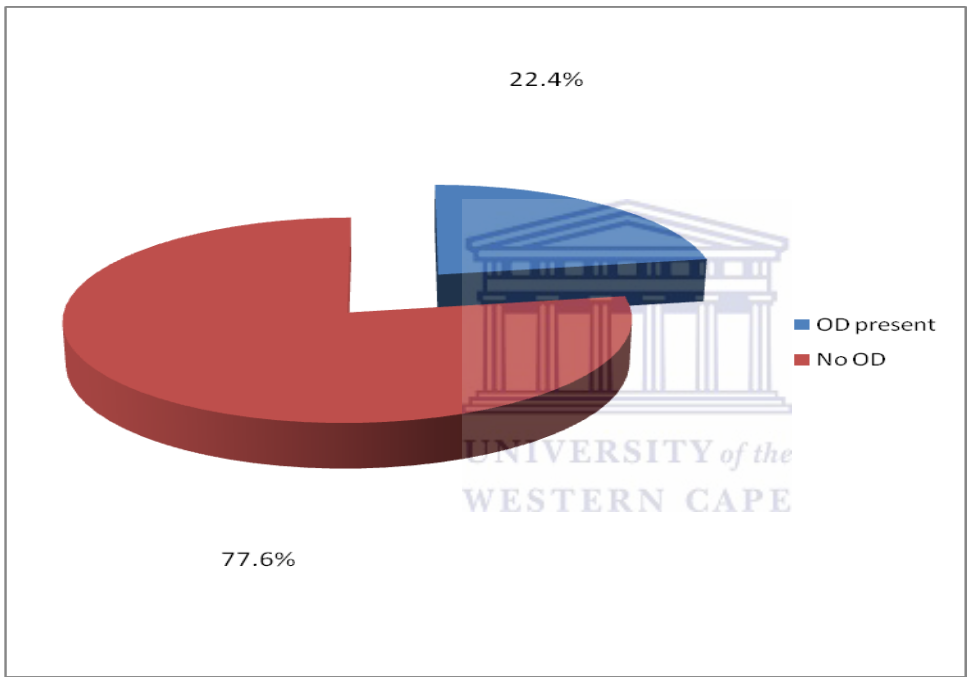

Fig. 4.2: Overall prevalence of opportunistic diseases in the study participants

OD= opportunistic disease

The prevalence of individual ODs is shown in Fig. 4.3. The most prevalent ODs were candidiasis, 29 (8.6%); TB, 26 (7.7%); and dermatitis 19 (5.6%). Other recorded ODs were chronic diarrhoea seen in 5 (1.5%), sepsis 5 (1.5%), cryptococcal meningitis 2 (0.6%), bacterial pneumonia 2 (0.6%), herpes zoster 2 (0.6%), genital herpes 2 (0.6%), genital warts 2 (0.6%), and Kaposi's sarcoma 1 (0.3%). In relative terms, candidiasis, TB and dermatitis, constituted 38.2%,

34.2%, and 25% of the ODs respectively. The pictures of some of the patients with externally visible ODs are shown in Appendix 8.

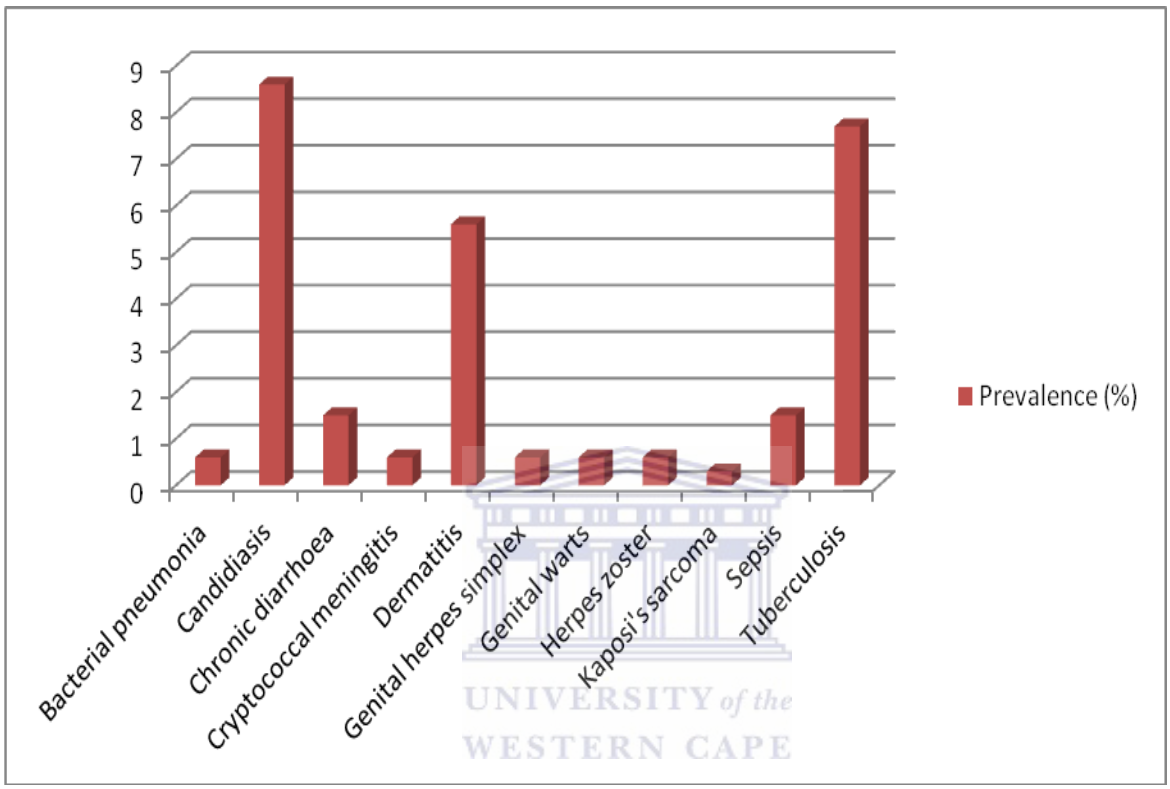

Fig. 4.3: Prevalence of individual opportunistic diseases in the study participants

Of the 76 patients in whom ODs were recorded, 52 (68.4%) had single ODs, 20 (26.3) had dual ODs while 1 person (1.3%) had triple ODs. The prevalence of dual/triple ODs among the study participants is shown in Fig. 4.4. The most prevalent dual OD condition was TB/candidiasis seen in 7 (2.1%) patients, followed by TB/dermatitis seen in 3 (0.88%) patients. TB/herpes zoster, candidiasis/chronic diarrhea, candidiasis/genital warts and candidiasis/dermatitis were each seen in 2 (0.59%) patients. The other dual/triple ODs were seen in only 1 (0.29%) patient and included candidiasis/dermatitis/sepsis, cryptococcal meningitis/genital herpes and candidiasis/genital herpes.

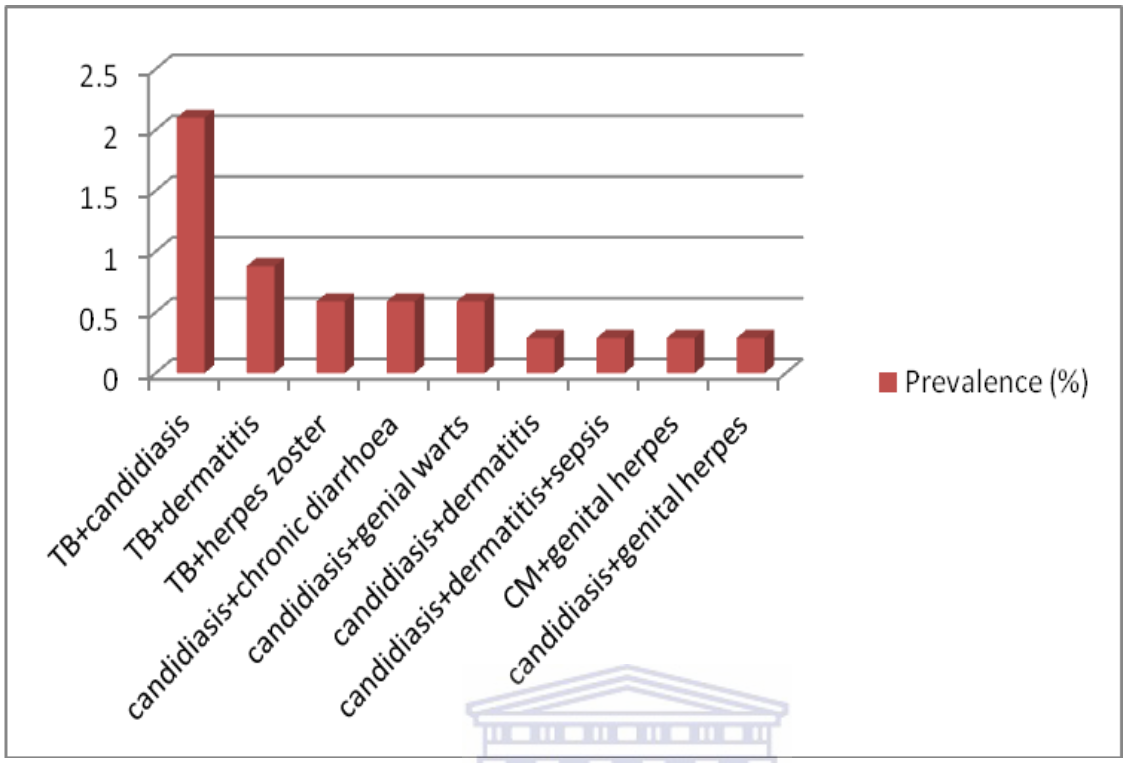

Fig. 4.4: Prevalence of dual/triple opportunistic diseases in the study participants

TB= tuberculosis; CM= cryptococcal meningitis

Among the three common ODs diagnosed, candidiasis was more prevalent in women (10.8%) than in men (4.3%). After excluding vaginal candidiasis, the prevalence of oral candidiasis was still slightly higher in women (6.3%) than in men (4.3%). Although the number of individuals with TB was equal in terms of gender, the prevalence of TB was higher in men, 13 (11.2%) compared to women, 13 (5.8%). Dermatitis was commoner in women with a prevalence of 7.2% compared to 2.6% in men. The prevalence of the three common ODs (candidiasis, TB and chronic dermatitis) by age groups is shown in Fig. 4.5. Candidiasis (23.5%) and dermatitis (11.8%) were most prevalent in participants ≤30 years while the prevalence of TB was highest in patients aged 41-50 years (11.3%).

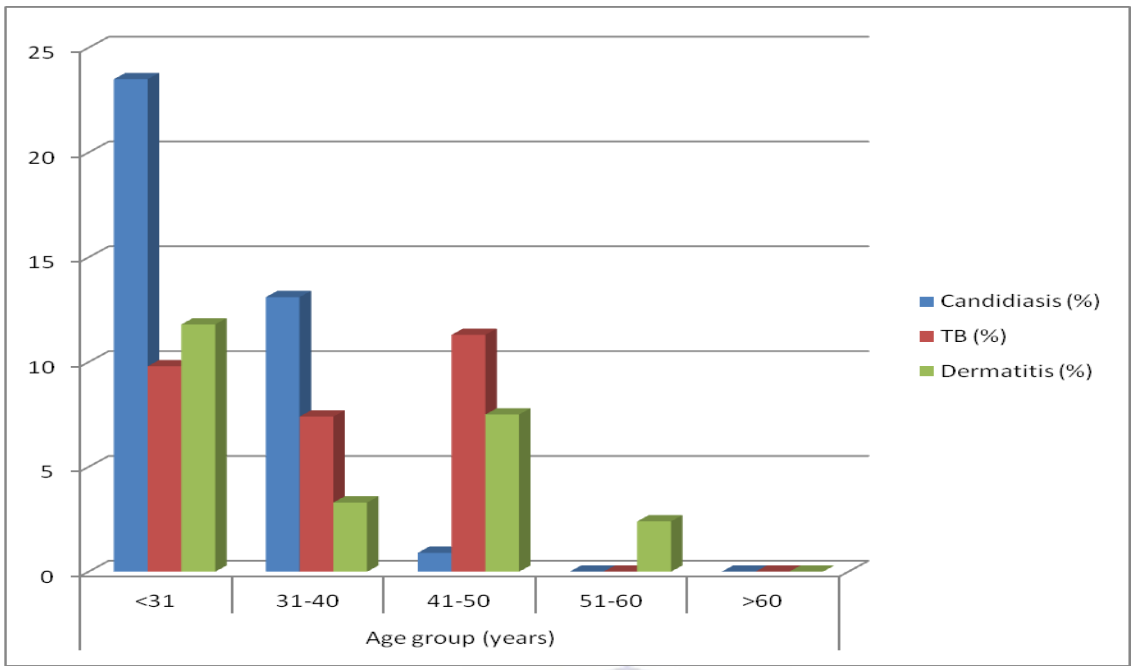

Fig. 4.5: Prevalence of common opportunistic diseases by age groups

4.4 Clinical details of the opportunistic diseases

The clinical details of the common ODs seen in the study participants are shown in Table 4.3. All the cases of candidiasis had *Candida albicans* as the isolate. In terms of site of candida lesion, oral candidiasis was predominant and either occurred alone, 12 (41.4%), or co-existed with vaginal candidiasis in women, 7 (24.1%).

Among the patients with TB, 11 (42.3%) were pulmonary while 9 (34.6%) were disseminated TB. All the cases of disseminated TB had clinical/radiological evidence of pulmonary involvement. The cases of extra-pulmonary TB involved the pleura (11.5%), lymph node (7.7%), and abdomen (3.8%). Of the 20 patients with evidence of pulmonary involvement, 9 (45%) had smear positive disease. The commonest symptoms in those with TB were weight loss (96.2%), fever (92.3%), and chronic cough (88.5%). Dermatitis was predominantly of fungal cause (63.2%).

Among the 5 patients with chronic diarrhoea, the isolates were *Cryptosporidium*, 2 (40%); *Giardia intestinalis* 2 (40%) while the remaining patient had no organism isolated. The bacterial isolates in the blood culture of the 5 patients with sepsis were *Salmonella typhi*, 2 (40%); *Klebsiella spp*, 2 (40%); and *Staphylococcus aureus*, 1 (20%). The 2 participants with bacterial pneumonia had *Streptococcus pneumoniae* isolated.

Among the three common ODs, the least median duration of HAART was seen in those with candidiasis (12 months) followed by TB (16 months). The lowest current median CD4 cell count was recorded in those with TB (165 cells/µl), followed by candidiasis (183 cells/µl). Dermatitis occurred at a relatively higher median CD4 cell count of 246 cells/µl.

Table 4.3: Clinical details of the common opportunistic diseases seen in the study participants

OD characteristics	
CANDIDIASIS (N=29)	
Site, n (%)	
Oral	12 (41.4)
Vaginal	10 (34.5)
Oral + Vaginal	7 (24.1)
Current CD4 cell count (cells/µl), median (IQR)	183 (142-427)
Duration of HAART (months), median (IQR)	12 (6-24)
TUBERCULOSIS (N=26)	
Site, n (%)	
Pulmonary	11 (42.3)
Pleura	3 (11.5)
Lymph node	2 (7.7)
Abdomen	1 (3.8)
Disseminated	9 (34.6)
Symptoms, n (%)	
Chronic cough	23 (88.5)
Fever	24 (92.3)
Weight loss	25 (96.2)
Night sweat	16 (61.5)
Sputum smear positivity†, n (%)	
Yes	9 (45.0)
No	11 (55.0)
Current CD4 cell count (cells/µl), median (IQR)	165 (85-216)
Duration of HAART (months), median (IQR)	16 (6-36)
DERMATITIS (N=19)	
Type, n (%)	
Fungal	12 (63.2)
Scabies	2 (10.5)
Non-infective	5 (26.3)
Current CD4 cell count (cells/µl) , median (IQR)	246 (144-392)
Duration of HAART (months), median (IQR)	41 (20-84)

†Sputum smear positivity refers to the 20 patients with evidence of pulmonary involvement

4.5: Risk factors for opportunistic diseases in the study participants

As shown in Table 4.4, the socio-demographic variables that had a significant association with the risk of OD on univariate analysis included the following: age ≤40 years (p=0.02), lower socio-economic class (p=0.03), household income <20,000 Naira (p=0.0002), and having >2 people per room (p=0.002). The risk of OD did not significantly differ according to gender, place of residence or marital status.

The univariate analysis of clinical risk factors for ODs is shown in Table 4.5. Occurrence of OD was significantly associated with HIV diagnosis <3 years (p<0.0001), duration of HAART <36 months (p<0.003), and HAART non-adherence (p<0.0001). The following baseline parameters were associated with increased risk of OD: WHO clinical stage 3-4 (p<0.0001), CD4 cell count < 200 cells/µl (p<0.0001), and haemoglobin <10 g/dl (p<0.0001). In addition, the risk of OD was significantly higher in participants with the following current parameters: CD4 cell count <200 cells/µl (p<0.0001), haemoglobin <10 g/dl (p<0.0001), and BMI <25 Kg/m^2 (0.047). There was no significant relationship between occurrence of OD and cotrimoxazole prophylaxis, diabetes, hypertension, alcohol consumption or smoking.

In order to determine the independent risk factors for OD, age, household income, residence, number of people per room, socio-economic status, duration of HIV diagnosis, HAART duration, HAART adherence, baseline WHO clinical stage, CD4 cell count (baseline and current), haemoglobin (baseline and current), and BMI were included in multivariate analysis (logistic regression) as they all had p<0.25 on univariate analysis. Although gender had a p-value of 0.58 on univariate analysis, it was also included in the logistic model as it was one of the variables considered *a priori* to be associated with OD risk. Finally, the independent risk factors for OD were household income <20,000 Naira, duration of HIV diagnosis <3 years, baseline WHO clinical stage 3-4, HAART non-adherence, baseline haemoglobin <10 g/dl, and current CD4 cell count <200 cells/µl (Table 4.6). The odds of having OD remained two times higher in participants ≤40 years but did not attain statistical significance (Adjusted odds ratio, AOR=1.89, 95% CI 0.92-3.89, p=0.08).

Table 4.4: Socio-demographic risk factors for opportunistic diseases (univariate analysis)

Variable	OD present N= 76 n (%)	No OD N = 278 n (%)	Odds ratio (95% CI)	p-value
Age (years)				
>40	28 (36.8)	138 (52.5)	1.0	
≤40	48 (63.2)	125 (47.5)	1.89 (1.12-3.20)	0.02
Gender				
Female	52 (68.4)	171 (65.0)	1.0	
Male	24 (31.6)	92 (35.0)	1.17 (0.68-2.01)	0.58
Socio-economic class				
Upper	2 (2.6)	25 (9.5)	1.0	
Middle	28 (36.8)	113 (43.0)	3.10 (0.69-13.86)	0.12
Lower	46 (60.5)	125 (47.5)	4.60 (1.05-20.19)	0.03
Residence				
Urban	38 (50.0)	153 (58.2)	1.0	
Rural	38 (50.0)	110 (41.8)	1.39 (0.83-2.32)	0.21
Marital status				
Single/separated/divorced/widowed	35 (46.1)	103 (39.2)	1.0	
Married	41 (53.9)	160 (60.8)	1.33 (0.79-2.22)	0.28
Household income (Naira, =N=)				
≥20,000	20 (26.3)	133 (50.6)	1.0	
<20,000	56 (73.7)	130 (49.4)	2.86	0.0002
People per room				
≤2	43 (56.6)	198 (75.3)	1.0	
>2	33 (43.4)	65 (24.7)	2.33 (1.36-3.98)	0.002

OD= opportunistic disease

Table 4.5: Clinical risk factors for opportunistic diseases (univariate analysis)

Variable	OD present N= 76 n (%)	No OD N = 278 n (%)	Odds ratio (95% CI)	p-value
HIV duration (years)				
≥3	35 (46.1)	187 (71.1)	1.0	
<3	41 (53.9)	76 (28.9)	2.88 (1.65-5.04)	<0.0001
Duration of HAART (months)				
≥36	26 (34.2)	140 (53.2)	1.0	
<36	50 (65.8)	123 (46.8)	2.19 (1.29-3.89)	0.003
HAART adherence				
Yes	35 (46.1)	228 (86.7)	1.0	
No	41 (53.9)	35 (13.3)	7.63 (4.30-13.55)	<0.0001
Cotrimoxazole prophylaxis				
Yes	66 (86.8)	231 (87.8)	1.0	
No	10 (13.2)	32 (12.2)	0.91 (0.43-2.04)	0.81
Baseline WHO clinical stage				
1-2	26 (34.2)	44 (16.7)	1.0	
3-4	50 (65.8)	219 (83.3)	9.48 (5.37-17.05)	<0.0001
Baseline CD4 cell count (cells/µl)				
≥200	20 (26.3)	151 (57.3)	1.0	
<200	56 (73.7)	112 (42.6)	3.76 (2.14-6.65)	<0.0001
Current CD4 cell count (cells/µl)				
≥200	38 (50.0)	226 (85.9)	1.0	
<200	38 (50.0)	37 (14.1)	6.11 (3.46-10.78)	<0.0001
Baseline haemoglobin (g/dl)				
≥10	41 (53.9)	222 (84.4)	1.0	<0.0001
<10	35 (46.1)	41 (15.6)	4.62 (2.64-8.10)	
Current haemoglobin (g/dl)				
≥10	58 (76.3)	245 (76.3)	1.0	
<10	18 (6.8)	18 (23.7)	4.22 (2.07-8.62)	<0.0001
BMI (current) [Kg/m^2]				
≥25	23 (30.3)	113 (43.0)	1.0	
<25	53 (69.7)	150 (57.0)	1.74 (1.01-3.00)	0.047
Diabetes				
Yes	1 (1.3)	10 (3.8)	1.0	
No	75 (98.7)	253 (96.2)	0.34 (0.02-2.06)	0.28
Hypertension				
Yes	9 (11.8)	43 (16.3)	1	
No	67 (88.2)	220 (83.7)	0.69 (0.30-1.45)	0.34
Alcohol consumption				
No	61 (80.3)	206 (78.3)	1.0	
Yes	15 (19.7)	57 (21.7)	0.89 (0.47-1.68)	0.72
Smoking				
No	69 (90.8)	246 (93.5)	1.0	
Yes	6 (9.2)	57 (21.7)	1.18 (0.45-3.11)`	0.73

BMI= body mass index; HAART= highly active antiretroviral therapy; OD= opportunistic disease; WHO= world health organisation

Table 4.6: Risk factors for opportunistic diseases (multivariate analysis)

	Adjusted Odds ratio	95% CI	P-value
Age ≤40 years	1.89	0.92-3.89	0.08
Household income <20,000 Naira	2.38	1.11-5.08	0.03
Duration of HIV diagnosis <3 years	2.12	1.05-4.24	0.004
Baseline WHO clinical stage 3-4	8.14	4.03-16.44	<0.0001
HAART non-adherence	5.42	2.63-11.18	<0.0001
Baseline haemoglobin <10g/dl	2.87	1.33-6.15	0.007
Current CD4 cell count <200 cells/µl	2.98	1.42-6.23	0.004

Corrected for *gender, residence, number of people per room, socio-economic class, HAART duration, BMI, baseline CD4 cell count, and current haemoglobin,*

HAART= highly active antiretroviral therapy; WHO= world health organisation

4.6 Specific associations of the common opportunistic diseases

The specific relationship between selected socio-demographic variables and each of the three common opportunistic diseases was further evaluated as shown in Tables 4.7-4.9. Rural residence was significantly associated with increased risk of dermatitis (p=0.02). Although candidiasis, TB, and dermatitis were all commoner in people of lower socio-economic class compared to middle and upper classes, none showed a statistically significant association (Table 4.8). The association of male gender with TB (p=0.08), and that of dermatitis with female gender (p=0.08) both fell short of attaining statistical significance.

Past history of TB treatment was a risk factor for current diagnosis of TB. Tuberculosis was diagnosed in 15 (20.5%) participants with a past history of TB compared to a TB prevalence of 4.7% in those without past history of TB, OR= 5.23, 95% CI 2.27-12.34, p<0.0001. The association between current diagnosis of TB and past history of TB remained significant after controlling for other relevant socio-demographic and clinical parameters in a multivariate analysis (Table 4.10), AOR= 5.30, 95% CI 1.39-20.21`, p=0.02.

Table 4.7: Relationship between gender and common opportunistic diseases

Specific OD	Male (N=116)	Female (N=223)	p-value
Tuberculosis			
Yes	13 (11.2)	13 (5.8)	0.08
No	103 (88.8)	210 (94.2)	
Candidiasis[†] (oral)			
Yes	5 (4.3)	14 (6.3)	0.45
No	111 (95.7)	209 (93.7)	
Dermatitis			
Yes	3 (2.6)	16 (7.2)	0.08
No	113 (97.4)	207 (92.8)	

[†] Patients with only vaginal candidiasis were excluded from this analysis since vaginal candidiasis is a disease of women; OD= opportunistic disease

Table 4.8: Relationship between socio-economic class and common opportunistic diseases

Specific OD	Socio-economic class			p-value
	Upper (N=27)	Middle (N=141)	Lower (171)	
Candidiasis				
Yes	1 (3.7)	9 (6.4)	19 (11.1)	0.21
No	26 (96.3)	132 (93.6)	152 (98.9)	
Tuberculosis				
Yes	1 (3.7)	7 (5.0)	18 (10.5)	0.13
No	26 (96.3)	134 (95.0)	153 (89.5)	
Dermatitis				
Yes	0 (0.0)	8 (5.7)	11 (6.4)	0.40
No	27 (100.0)	133 (94.3)	160 (93.6)	

OD= opportunistic disease

Table 4.9: Relationship between place of residence and common opportunistic diseases

Specific OD	Rural (N=148)	Urban (N=191)	p-value
Tuberculosis			
Yes	13 (8.8)	13 (6.8)	0.50
No	135 (91.2)	178 (93.2)	
Candidiasis			
Yes	13 (8.8)	16 (8.4)	0.89
No	135 (91.2)	175 (91.6)	
Dermatitis			
Yes	13 (8.8)	6 (3.1)	0.02
No	135 (91.2)	185 (96.9)	

OD= opportunistic disease

Table 4.10: Risk factors for tuberculosis (multivariate analysis)

Risk factors	Adjusted Odds ratio	95% CI	p-value
Past history of TB treatment	5.30	1.39-20.21	0.015
Duration of HIV diagnosis <3 years	0.1	0.01-0.71	0.022
HAART duration <36 months	8.15	1.15-57.66	0.036
HAART non-adherence	168.22	19.89-1422.62	<0.0001
Baseline CD4 cell count <200 cells/µl	31.35	2.79-351.57	0.005
Current haemoglobin <10g/dl	14.22	2.40-84.33	0.003

Corrected for *age, gender, number of people per room, household income, socio-economic class, smoking, HAART duration, BMI, current CD4 cell count, baseline haemoglobin, and baseline WHO clinical stage*

HAART= highly active antiretroviral therapy; TB= tuberculosis

CHAPTER FIVE

DISCUSSION

5.1 Discussion

This study determined the prevalence of opportunistic diseases in patients receiving HAART in a resource-limited setting in Nigeria and further highlighted the socio-demographic and clinical risk factors associated with their occurrence. In this study, the highest number of participants was between 31 and 40 years, an observation that has been corroborated by several studies both in developed and developing countries (Palella *et al*., 1998; Lawn, Badri & Wood, 2005; Srirangaraj & Venkatesha, 2011). This represents the bulk of the sexually active population which incidentally is the most economically productive age group. The tendency for HIV infection and its attendant complications to have their greatest impact on this group will definitely have a negative effect on the socio-economic achievements of SSA which is home to over 70% of the PLHIV globally. The majority of the participants were females. Some studies in West Africa have also shown a predominantly female HIV-infected population (Seyler, Toure, Messou, Bonard, Gabillard & Anglaret, 2005; Losina *et al*., 2007). This contrasts sharply with studies in Western countries, Asia and some parts of SSA which documented a male predominance (Forrest *et al*., 1998; Yazdanpanah *et al*., 2001; Sun *et al*., 2006; Komati *et al*., 2010). While the finding of this study is supportive of the female predominance among PLHIV in Nigeria (FMOH, 2010), it may also be reflective of a better health-seeking behaviour among women in a public HIV care and treatment centre. More than half of the participants belonged to the lower social class; and 55% had a monthly household income below 20,000 Naira which is about the national minimum wage in Nigeria. Although HIV is not necessarily a disease of the poor, Singh *et al.* (2003) and Lawn *et al.* (2005) also made a similar observation in India and South Africa respectively. Over 40% of the participants were rural dwellers despite the fact that the study site was in an urban area. This may be suggestive of limited availability of HIV care and treatment centres in rural areas in the country.

The baseline clinical characteristics show that 50% of the patients had advanced immunological disease at first presentation despite the observation that 72% had clinically mild disease at this

point based on WHO clinical staging. Several authors have shown that late immunological disease presentation has continued to be a problem among PLHIV in developing countries despite health education programmes and scaling up of ART (Sun *et al*., 2006; Losina *et al*., 2007; Daniyam *et al*., 2011). The median duration of HAART (3 years) paralleled the median duration of HIV diagnosis (3.4 years) which suggests a good time response between HIV diagnosis and HAART commencement. The HAART adherence rate of 78% is in agreement with the adherence rate of 77% reported across SSA in a meta-analysis (Mills *et al*., 2006). The 23.7% self-reported rate of past TB treatment in this study is in accordance with 14-37% reported elsewhere in developing countries (Lawn *et al*., 2005; Ghate *et al*., 2009; Komati *et al*., 2010).

The overall prevalence of ODs found in this study was 22.4%. This is in agreement with the rate of 20% documented by Corey *et al*. (2007) in a 5-year observational cohort study of 564 patients receiving HAART in Peru, South America. It is also comparable with the report of De Beaudrap *et al*., (2010) where 30% of their cohorts receiving HAART in Senegal, West Africa, developed ODs. Variable OD rates in patients on HAART have been reported in other settings, 8% in Thailand (Manosuthi *et al*., 2007); 8.3% in India (Srirangaraj & Venkatesha, 2011); 47.6% both in Taiwan (Sun et al., 2006) and South Africa (Mzileni, Longo-Mbenza & Chepha, 2008). The high rate of 47.6% found in Taiwan is double the rate in this study and sharply contrasts with the much lower rates of 8% in the other HAART-experienced Asian populations (Manosuthi *et al*., 2007; Srirangaraj & Venkatesha, 2011). Although the pre-HAART burden of ODs was not stated in most of the reports, the high rate of 47.6% in Taiwan may be attributable to the high OD prevalence of 77.7% in their patients before commencement of HAART. Mzileni *et al*. (2008) in South Africa studied a large cohort of 2,605 between 2004 and 2006 and found OD prevalence double that of this study although the focus of the study regarding ODs was on the 204 patients that died in that study. It is important to state that beyond differences in sample size and study design, as well as possible differences in pre-HAART OD burden between the cohorts of Mzileni *et al*. (2008) and the patients in this study, the 6-8 years time difference between their study and this study is a strong factor. Over this time, access to ART has significantly been scaled up both in South Africa and Nigeria so the findings of this study may be more reflective of the current trends of OD prevalence in sub-Saharan African patients enjoying a relatively better access to

HAART. The median duration of HAART at the time of determination of OD prevalence in Peru, Asia and South Africa ranged from 6 months to 3 years and this could have also contributed to the differences in OD prevalence across these developing countries.

Although the absolute prevalence rates for individual ODs were low in this study, candidiasis (8.6%), TB (7.7%), dermatitis (5.6%), chronic diarrhoea (1.5%) and sepsis (1.5%) were the most prevalent conditions. In relative terms, of the 76 patients diagnosed with ODs, candidiasis, TB, and dermatitis were suffered by 38.2%, 34.2%, and 25%, respectively. The most frequent ODs that occurred during HAART in the patients in this study are similar to those seen in patients receiving HAART in other low-income settings with TB, candidiasis, systemic bacterial infections being among the leading ODs (Sun *et al*., 2006; Mzileni, Longo-Mbenza & Chepha, 2008; Seyler, Messou, Gabillard, Inwoley, Alioum & Anglaret, 2007; De Beaudrap *et al*., 2010). The spectrum of ODs in HAART patients in this study is virtually similar to what was reported in HAART-naïve patients in Nigeria (Salami *et al*., 2006; Daniyam *et al*., 2011). Lack of change in the spectrum of ODs post-HAART has been observed by several authors (Forest *et al*., 1998; Ledergerber *et al*.; 1999; Sun *et al*., 2006; De Beaudrap *et al*., 2010). It is worth mentioning that unlike most of these studies, TB was not the commonest OD among our patients despite the well-known high burden of TB in Nigeria. It is possible that TB was under-diagnosed in our patients considering the difficulty associated with TB diagnosis in PLHIV especially in the absence of sputum mycobacterial cultures. This does not in any way undermine the fairly strict criteria that were employed in arriving at TB diagnosis in this study. TB diagnosis remains a challenge in PLHIV due to absence of classical features, high rate of smear negative disease, and relatively high burden of extra-pulmonary disease all of which are attributable to immunosuppression. This is not the case for candidiasis which is a lot easier to diagnose whether on clinical or laboratory grounds.

Compared to OD prevalence of 56.7 - 68.6% in HAART-naïve HIV-infected patients in Nigeria (Daniyam, Iroezindu, Shehu, Essien, Sati & Agaba, 2011; Saidu, Bunza, Abubakar, Adamu, Ladan & Fana, 2009; Salami, Olatunji & Oluboyo, 2006), the OD prevalence of 22.4% in this study suggests a decline in OD prevalence by 60-67% post-HAART in the Nigerian context. However, since there is no evidence that the pre-HAART burden of ODs among the patients in

this study carried out in Southern Nigeria is the same as the rates of 56.7-68.6% in HAART-naïve patients reported in the three studies in Northern Nigeria (Daniyam, Iroezindu, Shehu, Essien, Sati & Agaba, 2011; Saidu, Bunza, Abubakar, Adamu, Ladan & Fana, 2009; Salami, Olatunji & Oluboyo, 2006), this assumption cannot be stretched too far. In Senegal, De Beaudrap *et al*. (2010) reported an impressive decline in OD rate of 79% in their cohorts at the fourth year on HAART compared to their baseline OD burden. Unfortunately, this was not sustained beyond this time as the OD incidence began to rise by 5% per month after the fourth year. In Taiwan, the rate of OD decline was only 39% after 12 months of HAART. Despite the longer duration of HAART use in western countries, the rate of OD decline in the era of HAART has remained consistent and more impressive with over 80% decline in the rates of ODs (Palella *et al*., 1998; Lerdergerber *et al*., 1999; Kaplan *et al*., 2000). While it is not in doubt that that the relatively lower burden of ODs in the pre-HAART era, and widespread access to ART in high-income settings have reasonably contributed to this subtle difference, efforts to identify possible contributions of clinical and socio-demographic characteristics of PLHIV in developing countries is worthwhile.

A number of independent clinical risk factors for the occurrence of ODs were identified in this study including HIV duration less than 3 years, advanced WHO clinical stage at baseline, anaemia at baseline, current CD4 cell count less than 200 cells/µl, and HAART non-adherence. Similarly, the clinical risk factors for ODs in HAART–experienced patients in other studies include low level of current CD4 cell count, advanced baseline WHO clinical stage, and baseline anaemia (Lerdergerber *et al*., 1999; Kaplan *et al*., 2000; Lawn *et al*., 2005; De Beaudrap *et al*., 2010; Komati *et al*., 2010; Srirangaraj & Venkatesha, 2011). Additional clinical parameters which have also been identified as determinants of OD in patients receiving HAART include low baseline CD4 cell count, shorter duration of HAART, high viral load at baseline or in the course of treatment, and low BMI. Apart from viral load which was not quantified in this study due to economic constraints, the other additional factors were all significantly associated with the presence of ODs on univariate analysis in this study but their effect was not significant on multivariate analysis. It is possible that this study did not have enough power to investigate the association between some of these additional clinical parameters and risk of OD. The increased risk of OD associated with shorter duration of HIV infection has not been extensively

investigated especially in SSA. Considering that the scaling up of ART is relatively recent in SSA, it is possible that those who have had HIV infection for longer periods have possibly suffered more mortality following life-threatening ODs which could create the impression that the burden of OD is higher in those whose duration of HIV infection is shorter. Another possible argument is that if those who have had HIV infection for a longer duration have also received HAART much longer, then they are likely to have a more robust immune recovery and less likely to suffer HIV-related ODs. In this regard, a number of studies have found shorter duration of HAART to be associated with higher risk of OD (Lerdergerber *et al*., 1999; Hung & Chang, 2004; Losina *et al*., 2007).

The independent association between HAART non-adherence and occurrence of ODs documented in this study should be taken seriously. This observation was made despite the relatively good adherence with 78% of our patients taking 95% or more of their doses. While there is a tendency to focus on patient-related factors when HAART non-adherence is discussed in HIV treatment centres, we cannot afford to lose sight of the contribution of system failure in ART programmes. In 2004, the national ART programme of Nigeria suffered a major setback when it was hit by shortage of drugs (Monjok, Smesny, Okokon, Mgbere, & Essien, 2010). As a result, many patients were off drugs or staggered their dosages for up to 3 months which led to a structurally-induced adherence problem. Although the programme subsequently resumed when drug supplies were recommenced, till date, we probably do not know the exact contribution of that tragedy to antiretroviral treatment failure in Nigeria. In appreciation of the challenge non-adherence poses to the current benefits of HAART, Yazdanpanah *et al*. (2001) declared: "moreover, due to issues of adherence, resistance, failure and cross-resistance, there will likely be many patients who remain at major risk for the development of opportunistic infections [in the era of HAART]."

Another important finding was that past history of TB treatment was an independent risk factor for TB, an observation that was also reported by Syler *et al*. (2005). While Komati *et al*. (2010) identified past history of TB to predict TB occurrence during HAART on univariate analysis, this association was not upheld after controlling for other factors. On the other hand, Lawn *et al*. (2005) found no association between past history of TB and TB occurrence during HAART. As

suggested by Seyler *et al*. (2005): "reporting a higher incidence of TB in patients with a history of TB inevitably leads to question if the TB episodes were more frequent relapses from persistent bacilli rather than re-infection with new bacilli occurring since the previous episode."

In developed nations, emphasis on the risk factors for ODs has largely been on clinical parameters which have led to baseline CD4 cell count and post-treatment CD4 cell count being acknowledged as the strongest predictors of HIV-related OD (Ledergerber *et al*., 1999; Kaplan, Hanson, Jones & Dworkin, 2001). SSA with its long list of socio-economic determinants of health cannot afford to endlessly tow this line. In this study, poor household income was found to be an independent predictor of ODs. Although lower socio-economic class was a strong predictor of OD on univariate analysis, this effect was lost after controlling for other factors. It may also be noteworthy that overcrowding (having more than 2 people per room) which is an index of poverty was associated with increased OD risk on univariate analysis. According to Lawn *et al*. (2005) socio-economic class was not found to have a significant impact on TB risk in South African cohorts. Nevertheless, overcrowding and poor hygiene have been suggested as contributory factors to high burden of OD in developing countries (Srirangaraj & Venkatesha, 2011). Bearing in mind the finding of this study, household income on its own may be more intimately associated with health challenges than other factors such as educational status and occupation which in addition to income contribute to the socio-economic designation of the individual. If the relationship between poverty and OD risk in low-income countries is supported by more studies, PLHIV in Nigeria will be in great danger of ODs considering that 55% of the participants of this study had a household income below the national minimum wage.

Furthermore, younger patients (≤40 years) tended to be at an increased risk of ODs. While Lawn *et al.* (2005) demonstrated increased risk of TB in younger patients (<33 years), Ghate *et al*. (2009) in a predominantly HAART-naïve population in India reported that older age was a strong determinant of ODs. Pallela *et al.* (1998) found no association between age and OD risk in a cohort of US patients. In line with the observations of Pallela *et al.* (1998) and Lawn *et al.* (2005), we did not find gender to be a strong risk factor for ODs. Contrarily, male gender was found to be strongly associated with the occurrence of ODs in other reports (Manosuthi *et al*., 2007; Komati *et al*., 2010). Large prospective cohort studies are needed to investigate the

association between socio-demographic variables and HIV-related ODs in the era of HAART in developing countries.

5.2 Limitations

This study had some limitations which include the following:

1. HIV viral load of the patients was not carried out. This is due to the fact that HIV treatment programmes in Nigeria are running on very tight budgets for over two years such that HIV viral load which is very expensive (running cost of $66 per sample) is no longer done except for initial evaluation prior to commencement of HAART in a few selected centres.
2. The diagnosis of herpes zoster and genital warts were entirely based on clinical grounds. In addition, some relatively less common HIV-related ODs in SSA for which diagnostic facilities are not readily available such PCP, MAC and CMV disease were not diagnosed. Although a high index of suspicion was maintained for PCP, none of the participants met the clinical criteria for its presumptive diagnosis.
3. It was not possible to do sputum mycobacterial culture for the diagnosis of pulmonary TB which would have significantly increased the sensitivity of pulmonary TB diagnosis. This is due to the high cost of the test and its non-availability in South-east Nigeria. However, the TB screening and diagnostic algorithm in HIV-infected patients was combined with sputum AFB test, radiological investigations and treatment response (in some cases) to improve the sensitivity of TB diagnosis.
4. The impact of antiretroviral drug resistance was not determined as the sophisticated facilities for antiretroviral resistance testing are not available in most parts of Nigeria. In the few places this could be done, the cost is usually prohibitive.
5. The relatively small number of patients with TB in this study may call for cautious interpretation of our findings regarding the risk factors associated with TB on multivariate analysis. For example, duration of HIV diagnosis less than 3 years surprisingly comes across as protective of TB while the odds ratio for HAART non-adherence as a TB risk factor is extremely high.

6. Cotrimoxazole use had no effect on the occurrence of ODs on univariate analysis and subsequently was not included in the logistic regression model. Cotrimoxazole use is known to improve morbidity and mortality in PLHIV (Walker *et al*., 2010). While this observation may be considered as a potential limitation of this study, it is possible that some of the patients whose pharmacy records captured that they were on cotrimoxazole prophylaxis were actually not consuming the drug.

CHAPTER 6

CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

In this mini-thesis, the prevalence of HIV-related opportunistic diseases (ODs) was determined among patients receiving HAART in a resource-limited setting in Nigeria. The clinical and socio-demographic risk factors of the HAART patients were also described and their associations with the occurrence of ODs were investigated. The overall prevalence of ODs was found to be 22.4% which is within the range of 8-48% reported in HAART-experienced patients in low-income countries. Among the 76 patients diagnosed to have ODs, candidiasis (38.2%), TB (34.2%), dermatitis (25%), chronic diarrhoea (6.6%) and sepsis (6.6%) were the leading conditions. While this may be suggestive of some reasonable decline in OD prevalence compared to studies in HAART-naïve groups in Nigeria, the spectrum of ODs has largely remained the same.

Fifty one percent (51%) of the participants were ≤40 years, and the majority of them were females (65.8%). Over 40% of the participants were rural dwellers, 50.4% belonged to the lower socio-economic class, and 55% had a monthly household income below 20,000 Naira. The baseline clinical characteristics showed that 50% of the patients had advanced immunosuppression at first presentation despite the observation that 72% had clinically mild disease at this point based on WHO clinical staging. The median duration of HAART (3 years) paralleled the median duration of HIV diagnosis (3.4 years) and HAART adherence rate was high with 78% of patients being adherent. Past history of TB treatment was reported by 23.7%. The independent risk factors for the occurrence of ODs were poor household income, HIV duration less than 3 years, advanced WHO clinical stage at baseline, anaemia at baseline, low level of current CD4 cell count, and HAART non-adherence. In addition, younger age tended to be associated with increased risk of OD. Past history of TB was found to be a strong predictor of TB. These findings suggest that ODs remain a challenge in patients receiving HAART in Nigeria. Beyond the well recognised clinical predictors of HIV-related ODs, poverty may emerge a strong determinant of HIV-related ODs in developing countries.

6.2 Recommendations

Based on the findings of this study, the following recommendations are put forward:

1. A high index of suspicion should be maintained for opportunistic diseases in PLHIV despite the use of HAART considering that one-fifth of patients receiving HAART in this study were found to have at least one opportunistic disease.
2. Health education on HIV screening and early presentation should be intensified to encourage early diagnosis, and prompt access to HIV care and treatment. This is because individuals who presented late for the first time (i.e at an advanced WHO clinical stage) were found to be eight times more likely to come down with an opportunistic disease while on HAART compared to those who presented when their clinical disease was mild.
3. Anaemia should be properly investigated for during baseline evaluation in PLHIV and when present should be appropriately corrected to achieve normal haemoglobin concentrations. This is because patients who were anaemic pre-HAART were found to have a three times increased risk of suffering opportunistic diseases after commencement of HAART independent of immunological recovery.
4. Individuals who continue to have low CD4 cell count while on HAART should be aggressively evaluated for opportunistic diseases and practical efforts to optimize their immunological recovery should be made which may involve evaluation for drug resistance followed by appropriate drug switch.
5. As recommended by WHO/TB-HIV Working Group (WHO, 2011), active case finding for TB and wide use of isoniazid preventive therapy in eligible HIV-infected patients should be widely promoted.
6. Prophylaxis for fungal infections especially candidiasis should be widely implemented in the routine management PLHIV in endemic regions such as SSA after exclusion of active disease, irrespective of HAART use. This can be standardized as the widely practiced cotrimoxazole prophylaxis whose benefits have been impressive.
7. Low-income groups should become a target for a more aggressive evaluation for HIV-related opportunistic diseases. While HIV/AIDS is not necessarily a disease of the poor,

this study found that individuals earning below the Nigerian national minimum wage were twice more likely to suffer opportunistic diseases.

8. HAART adherence counselling should be intensified in patients receiving HAART. Management of adherence problems may involve identifying the peculiar individual, social, and structural factors affecting HAART adherence with a view to addressing them. Measures that may be instituted could include use of treatment partners, use of alarm reminders, reducing pill burdens, and drug switch following non-tolerable side effects. The need for improved commitments of indigenous governments in SSA towards sustained availability and accessibility of ART cannot be overemphasized.

9. Earlier initiation of HAART before progression to advanced immunosuppression should be encouraged in order to decrease the likelihood of opportunistic diseases.
10. Use and adherence to Cotrimoxazole prophylaxis should continue to be encouraged until patients on HAART achieve sustained immunological recovery as recommended by WHO guidelines (WHO, 2006).

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APPENDIX 1: UWC ETHICAL APPROVAL LETTER

UNIVERSITY of the
WESTERN CAPE

OFFICE OF THE DEAN
DEPARTMENT OF RESEARCH DEVELOPMENT

28 March 2012

To Whom It May Concern

I hereby certify that the Senate Research Committee of the University of the Western Cape has approved the methodology and ethics of the following research project by:
Dr M Iroezindu (School of Public Health)

Research Project:	**Prevalence of HIV-related opportunistic diseases amongst HAART patients at the Federal Medical Centre in Oweri, Nigeria.**
Registration no:	**11/10/42**

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

Private Bag X17, Bellville 7535, South Africa
T: +27 21 959 2948/2949 . F: +27 21 959 3170
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APPENDIX 2: FMC OWERRI ETHICAL APPROVAL LETTER

FEDERAL MEDICAL CENTRE

P. M. B. 1010,Orlu Road Owerri, Imo State, Nigeria

Medical Director/CEO
Dr. A. C. Uwakwem
MBBS, FWACS, FICS, FICA. IMAAO
Chief Consultant Ophthalmologist

Head of Clinical Services
Dr. E. C. Osuagwu
MBBS, FWACS
Chief Consultant (Obstetrics & Gynaecology)

Chairman of Board
Prof. Ivara Ejemot Esu, OFR
B.Sc, (Ife) M.Sc (Minnesota) PhD (ABU)
Fellow, Soil Science Society of Nigeria

Head of Administration Services
Mrs. Nnenna Onyegbula
B.Sc. MPA, AHAN

e-mail: fmcowerri@yahoo.com
Phone:08191365555, 08033411575 (MD), 08033362578 (HAS), 08035531242 (HCS)

05182

FMC/OW/HCS/VOL.II

14th Sept. 2011

Dr. M.O. Iroezindu
Consultant Physician
Department of Internal Medicine
Federal Medical Centre
Owerri

Dear Dr. Iroezindu

APPLICATION FOR ETHICAL CLEARANCE
RE: HIV-RELATED OPPORTUNISTIC DISEASES IN THE ERA OF HAART AT THE FEDERAL MEDICAL CENTRE, OWERRI

Your application for ethical clearance in respect of the above-captioned study was received and considered by the Ethical Committee.

I am glad to inform you that provisional approval has been granted for the study to be embarked upon pending ratification at the next meeting of the committee.

Please note that you are expected to submit a copy of your concluded work to the Ethical Committee.

Dr. E.C.Osuagwu
HEAD OF CLINICAL SERVICES/CHAIRMAN ETHICAL COMMITTEE

APPENDIX 3

UNIVERSITY OF THE WESTERN CAPE

School of Public Health

Private Bag X17 ● **BELLVILLE** ● 7535 ● South Africa

Tel: 021- 959 2809, Fax: 021- 959 2872

PARTICIPANT INFORMATION SHEET

I am *Iroezindu Michael*, a student studying for the Masters in Public Health degree at the University of the Western Cape, South Africa. I am gathering information in the form of a research from people living with HIV/AIDS on treatment who are 15 years and above. I am trying to find out the types of unusual infections and cancers (known as *opportunistic diseases*) that occur in this group of people and the risk factors that make them occur**.** The study will be used for obtaining a Masters degree. In addition, the findings may lead to recommendations that may improve patient management. I would like to ask you some questions, conduct physical and laboratory examination which will take about 15-30 minutes of your time. Samples of blood, skin and other body fluids may be collected from you and the process of obtaining some samples such as blood may cause transient discomfort. You may choose not to participate in this study and you also have the freedom to withdraw from the study if you so desire and this will not affect you or your treatment in any way. Your identity, contact details and any information you give me will not be disclosed to anyone. *Below is the Igbo language version of this participant information.*

Researcher's name: IROEZINDU MICHAEL.

Address: DEPARTMENT OF MEDICINE, FEDERAL MEDICAL CENTRE, OWERRI, NIGERIA.

Telephone: +2347031376345, +2348028614747.

E-mail: mikezindu@yahoo.com

Should you have any questions regarding this study or wish to report any problem you have experienced related to the study, please contact the study supervisors (see below)

APPENDIX 4

UNIVERSITY OF THE WESTERN CAPE

School of Public Health

Private Bag X17 ● **BELLVILLE** ● 7535 ● South Africa
Tel: 021- 959 2809, Fax: 021- 959 2872

IHE ONYEOBULA KWESIRI IMA

Aha m bu *Iroezindu Michael*, nwa akwukwo na-acho inweta akara nke Masters na Public Health na University of the Western Cape, South Africa. Ana m eme ihe omumu research gbasara ndi nwere Oria Obere n'aja ocha ndi na-anu ogwu ndi di afo iri na ise ma o bu karia. Ihe m na-achoputa bu maka oria ndi digasi anaa a na-akpo o*ppotunistic diaseases*. Nchoputa a ga-enyere m aka i nmeta akara Masters. Ozokwa, o ga-enyekwa aka ime ka ogwugwo ndi oria obere na-aja ocha di nma karia. A ga m aju gi ufodu ajuju, lee gi ahu ma mee kwa gi ule obara na ule ndi ozo di iche iche nke ga-ewe oge nwere ike rue nkeji hour. Imiri obara nwere ike ifu gi obere ufu nwa mgbe nta. I nwere ike isi na ihe omumua a masighi gi ma obukwa wepu onwe gi oge obula ichoro ma o nweghi ihe obula nke a ga-ebutere gi. Onweghi onye obula a ga-agwa ihe gbasara gi.

Aha onye na-eme nchoputa: IROEZINDU MICHAEL.
Addressi: DEPARTMENT OF MEDICINE, FEDERAL MEDICAL CENTRE, OWERRI, NIGERIA.
Ekwe nti: +2347031376345, +2348028614747.
E-mail: mikezindu@yahoo.com.

O buru na i choro iju ajuju ozo ma obu n'inwere nsogbu nihi nchoputa a, i nwere ike ime ka ndi isi ihe nchoputa a mara. E dere aha ha n'okpuru ebe a.

Supervisor's Name: Prof. Harry Hausler
University of the Western Cape
Private Bag X17, Belville 7535
South Africa.
Cell: +2782 779 0045
Email: hhausler@tbhivcare.org

Co-supervisor's Name: Dr. Brian Van Wyk
University of the Western Cape
Private Bag X17, Belville 7535
Telephone: +2721959-2173
Cell: +2782 911 0904
Fax: +27 21 959 2872
Email: bvanwyk@uwc.ac.za

If you are willing to participate in the study, please read and sign the consent form below.

APPENDIX 5

RECORD OF AN INFORMED CONSENT TO CONDUCT AN INTERVIEW

Date: …….

Interviewer's name: *IROEZINDU MICHAEL*

Tel: +2347031376345 or + 2348028614747

UWC Student no: 3002900
E-mail: mikezindu@yahoo.com

Institution: *University of the Western Cape*

Interviewees' pseudonym:_____

Interview site: *Heart to Heart Centre, Federal Medical Centre, Owerri*.

Thank you for agreeing to allow me interview you. What follows is an explanation of the purpose and process of this interview. You are advised to give your consent to participate in this interview which will involve asking you some questions, conducting a physical examination on you and collecting your blood sample (and samples from other body parts if required) for laboratory investigations. This data will be used for my research to acquire a Masters degree at the School of Public Health, University of the Western Cape, South Africa.

1. **Information about the interviewer**: I am *Iroezindu Michael*, a student at the School of Public Health, University of the Western Cape. As part of my Masters in Public Health, I am required to carry out a research and write a report. I will be focusing on HIV-related opportunistic diseases in the era of HAART in a resource-limited setting. I am accountable to my supervisors; Hausler Harry and Van Wyk Brian.

2. **Purpose of interview**: The purpose of my interview is to fulfill the part of my Masters in Public Health. The content will be questions that will centre on finding out about opportunistic

diseases in HIV-infected patients on HAART. The research will culminate into writing a report for the Masters in Public Health degree of University of the Western Cape.

3. **The interview process:** Will involve getting a clearance, an interviewee, consent signing to participate, questionnaire administration, physical examination and laboratory investigation.

4. **Anonymity of contributors**: At all times, I will keep the source of the information confidential and refer to you or your words by a pseudonym or invented name which I would like you to choose. I shall keep any or the record of your participation locked away at all times, and destroy them after the data has been collected.

5. **Things that may affect your willingness to participate**: The interview may touch on issues which may affect your willingness to participate. If there is anything that you would prefer not to respond to, please feel free to say so. I will not be offended and there will be no negative consequences if you would prefer not to answer a question. I would appreciate your guidance should I ask anything which you see as intrusive.

6**. Agreement**

6.1. Interviewee's agreement

The respondent will be asked to give his/her consent in writing or thumb printing

6.2. **Interviewee's agreement**

I shall keep the contents of the above research interview confidential in the sense that the pseudonym noted above will be used in all documents which refer to the interview. The contents will be used for the purposes referred to above, but may be used for published or unpublished research at a later stage without further consent. Any change from this agreement will be renegotiated with you. If you are willing to participate in the study please sign below.

Participant's signature/thumbprint Date_____ Venue _____

Witness signature/thumbprint Date_____ Venue _____

Investigators signature Date_____Venue _____

Appendix 6: Questionnaire

PREVALENCE OF HIV-RELATED OPPORTUNISTIC DISEASES AMONGST HAART PATIENTS AT THE FEDERAL MEDICAL CENTRE IN OWERRI, NIGERIA

NOTE: Kindly respond to the following questions by filling the boxes using the relevant codes provided beside each box where applicable.

SECTION 1: **SOCIO-DEMOGRAPHIC DATA**

1. Patient's File Number: ☐☐ ☐☐ ☐☐

2. What is your **Gender**? ☐ Male=1, Female =2

3. What is your **age** (in years)? _____

4. What is your **marital status**? ☐ Single=1, Married=2, Separated/Divorced=3, Widowed=4

5. What is your **ethnicity**? ☐ Igbo=1, Hausa/Fulani=2, Yoruba=3, Southern minorities=4, Northern minorities=5,

6a. What is your **occupation**? ☐ Civil Servant=1, Trader=2, Farmer=3, Student=4 Housewife =5, Technician=6, Others=7, Unemployed=8

6b. What is the **occupation of your spouse**? (Indicate the occupation of your father instead if you are under the care your parents)

☐ Civil Servant=1, Trader=2, Farmer=3, Student=4 Housewife =5, Technician=6, Others=7, Unemployed=8

7a. What is your highest **educational level?** ☐ None=1, Informal=2, Primary=3, Secondary =4, Tertiary =5

7b. What is the highest **educational level of your spouse?** (Indicate that of your mother instead if you are under the care your parents)

☐ None=1, Informal=2, Primary=3, Secondary =4, Tertiary =5

8. What is the nature of your place of **residence**: ☐ Rural=1 Urban =2

9. How many rooms do you have in your apartment? ☐ 1 room =1, 2 rooms =2,

3 rooms =3, ≥ 4 rooms = 4

10. How many people share your room with you? ☐ None=1, 1 person =2, 2 persons =3, ≥ 3 persons =4

11. What is your household monthly income? ☐ < N20, 000 =1; N20, 000-50,000 = 2,

N51, 000-100, 000 = 3; > N100, 000 = 4

12. How many people are dependent on your household income?

☐ None =1, ≤ 4 people =2, 5-8 people =3, >8 People = 4

13. Socio-economic class: ☐ *To be completed by the researcher as Class 1, 2, 3, 4 or 5 using information obtained from numbers 6-12 above.*

SECTION 2: CLINICAL INFORMATION

History

14. Kindly indicate if you have any of these medical complaints listed below including the duration of the complaint.

i) Fever ☐ Yes=1, No=2, duration……(specify days/weeks/months)

ii) Cough ☐ Yes=1, No=2, duration……(specify days/weeks/months)

iii) Weight loss ☐ Yes=1, No=2, duration……(specify days/weeks/months)

iv) Night sweats ☐ Yes=1, No=2, duration……(specify days/weeks/months)

v) Diarrhoea ☐ Yes=1, No=2, duration……(specify days/weeks/months)

vi) Headache ☐ Yes=1, No=2, duration……(specify days/weeks/months)

vii) Neck pain ☐ Yes=1, No=2, duration……(specify days/weeks/months)

viii) Skin rashes/growth ☐ Yes=1, No=2, duration……(specify days/weeks/months)

ix) White patches in the mouth ☐ Yes=1, No=2, duration….. (specify days/weeks/months)

x) Mouth ulcers ☐Yes=1, No=2, duration……(specify days/weeks/months)

xi) Ulcers in the genitals ☐Yes=1, No=2, duration……(specify days/weeks/months)

xii) Vaginal or penile discharge ☐Yes=1, No=2, duration……..(specify days/weeks/months)

xiii) Others (Specify)……, duration……..(specify days/weeks/months)

15. Duration of HIV diagnosis (in years) _____(specify number of months if < 1 year)

16. Duration of ART (in months) _____

17. ART adherence in the past 6 months ☐ Yes=1 No=2

(Answer Yes/No with respect to your duration of ART if less than 6 months)

18. Are you taking Co-trimoxazole prophylaxis? ☐ Yes=1 No=2

19. Co-trimoxazole adherence in the past 6 months? ☐ Yes=1 No=2 (Answer Yes/No with respect to the duration if less than 6 months)

20. Have you had TB treatment in the past? ☐ Yes=1 No=2

20. Do you smoke cigarette? ☐ Yes=1 No=2

22. Do you take alcohol? ☐ Yes=1 No=2

PHYSICAL FINDINGS AND DIAGNOSIS

23. Anthropometry:

a) Height…….. (m), b) Weight…… (Kg), c) Body Mass Index (BMI)……. (Kg/m^2)

24. General examination…….

25. Skin abnormalities…….

26. CNS findings……

27. Respiratory findings ……

28. Abdominal findings…….

29. CVS findings……

30. Opportunistic disease (OD) clinical diagnosis made

a) …….

b) …… ……

c) …….

31. WHO clinical stage at baseline: 1☐ 2☐ 3☐ 4☐

SECTION 3: LABORATORY INVESTIGATIONS

32. CD4 cell count (cells/µl): baseline……., Current…….

33. Sputum Smear for AFB (x3)

Sample 1 ☐ Positive=1 Negative=2

Sample 2 ☐ Positive=1 Negative=2

Sample 3 ☐ Positive=1 Negative=2

Final interpretation of Sputum AFB ☐ Positive=1 Negative=2

34. Complete blood count + ESR

Haemoglobin (g/dl)……

WBC (x 10^6/l):

Total……

Differential: Neutro….., Lympho…….,Mono……, Eosino……, Baso……

Platelet count (x 10^6/l)…….

ESR (mm/hour)……

35. Culture results (Specify specimen)……

36. CSF findings……

37. Histology report (Specify specimen)…….

38. Chest X-ray findings……..

39. Others (specify)…….

APPENDIX 7: WHO CLINICAL STAGING (WHO, 2005)

WHO Staging System for HIV Infection and Disease in Adults and Adolescents
Current or past history of any of the conditions described

Clinical Stage I: 1. Asymptomatic 2. Current or past history of persistent generalized lymphadenopathy (PGL) *Performance scale 1: Asymptomatic, normal activity*
Clinical Stage II - current or past history of: 3. Weight loss, ≤ 10% of body weight 4. Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular chelitis) 5. Herpes zoster within the last 5 years 6. Recurrent upper respiratory tract infections (i.e. bacterial sinusitis) *And/or Performance scale 2: Symptomatic, normal activity*
Clinical Stage III – current or past history of: 7. Weight loss > 10% of body weight 8. Unexplained chronic diarrhea > 1 month 9. Unexplained prolonged fever (intermittent or constant) > 1 month 10. Oral candidiasis (thrush) 11. Oral hairy leukoplakia 12. Pulmonary tuberculosis within the past year 13. Severe bacterial infection (i.e. pneumonia, pyomyositis) *And/or Performance scale 3: bed-ridden < 50% of the day during the past month*
Clinical Stage IV – current or past history of: 14. HIV wasting syndrome[1] 15. Pneumocystis carinii pneumonia 16. CNS toxoplasmosis 17. Cryptosporidiosis with diarrhea > 1 month 18. Extrapulmonary cryptococcosis 19. Cytomegalovirus (CMV) disease of an organ other than liver, spleen or lymph nodes 20. Herpes simplex virus (HSV) infection, mucocutaneous > 1 month, or visceral any duration 21. Progressive multifocal leukoencephalopathy (PML) 22. Any disseminated endemic mycosis (i.e. histoplasmosis, coccidiodomycosis) 23. Candidiasis of the esophagus, trachea, bronchi or lungs 24. Disseminated atypical mycobacterium 25. Non-typhoid Salmonella septicemia 26. Extrapulmonary tuberculosis 27. Lymphoma 28. Kaposi's sarcoma (KS) 29. HIV encephalopathy[2] *And/or Performance scale 4: bed-ridden > 50% of the day during the last month*

[1] HIV wasting syndrome: weight loss of > 10% body weight, plus either unexplained chronic diarrhea (> 1 month), or chronic weakness and unexplained prolonged fever (> 1 month).
[2] HIV encephalopathy: clinical findings of disabling cognitive and/or motor dysfunction interfering with activities of daily living progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection that could explain the findings)

APPENDIX 8

PICTURES OF SOME EXTERNALLY VISIBLE OPPORTUNISTIC DISEASES IN THE STUDY PARTICIPANTS

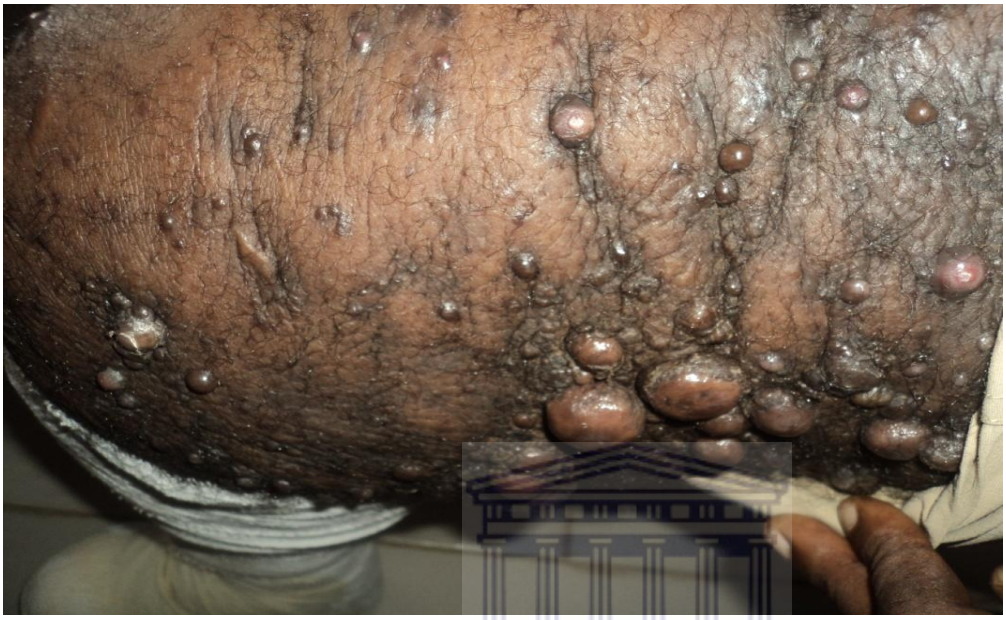

Fig. i: Kaposi's sarcoma affecting the right lower limb in a 46 year old man on HAART

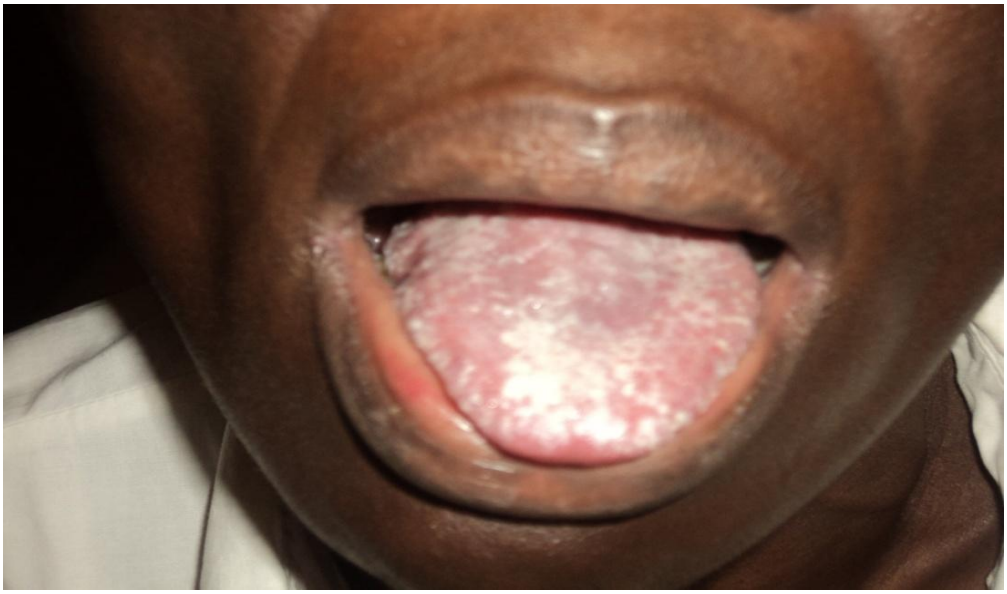

Fig. ii: Oral candidiasis in a 38 year old woman on HAART

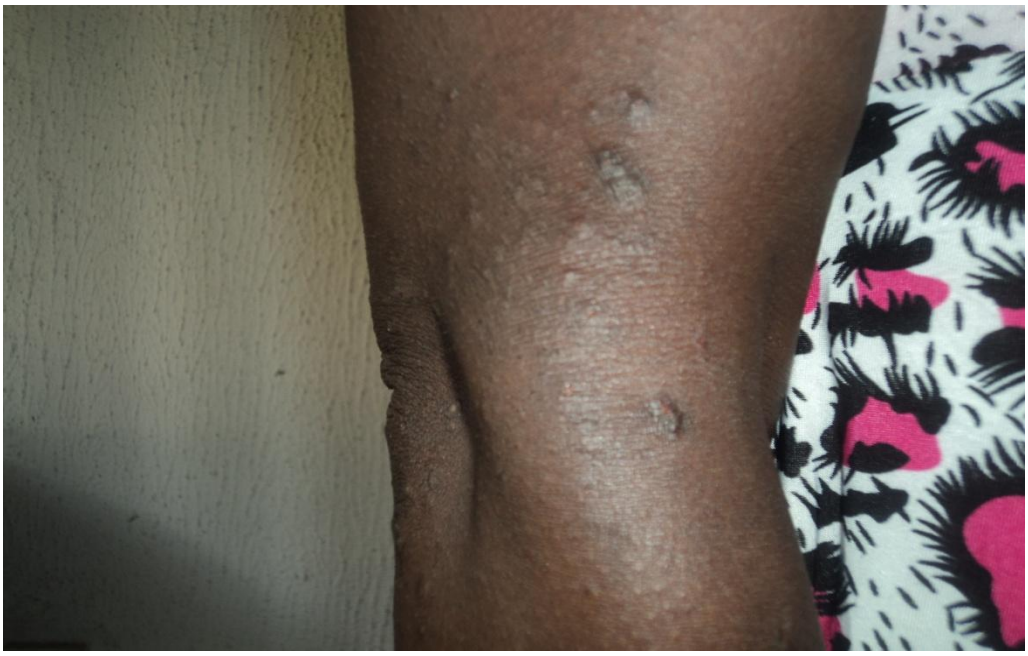

Fig. iii: Dermatitis (non-infective) in a 29 year old woman on HAART

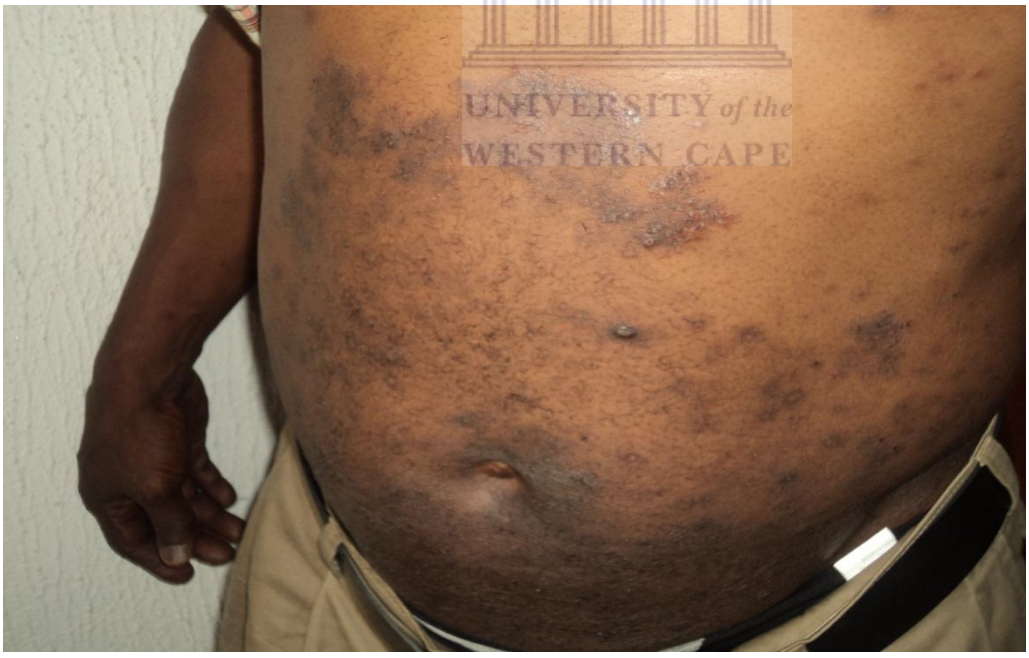

Fig iv: Dermatitis (Fungal) in a 49 year old man on HAART

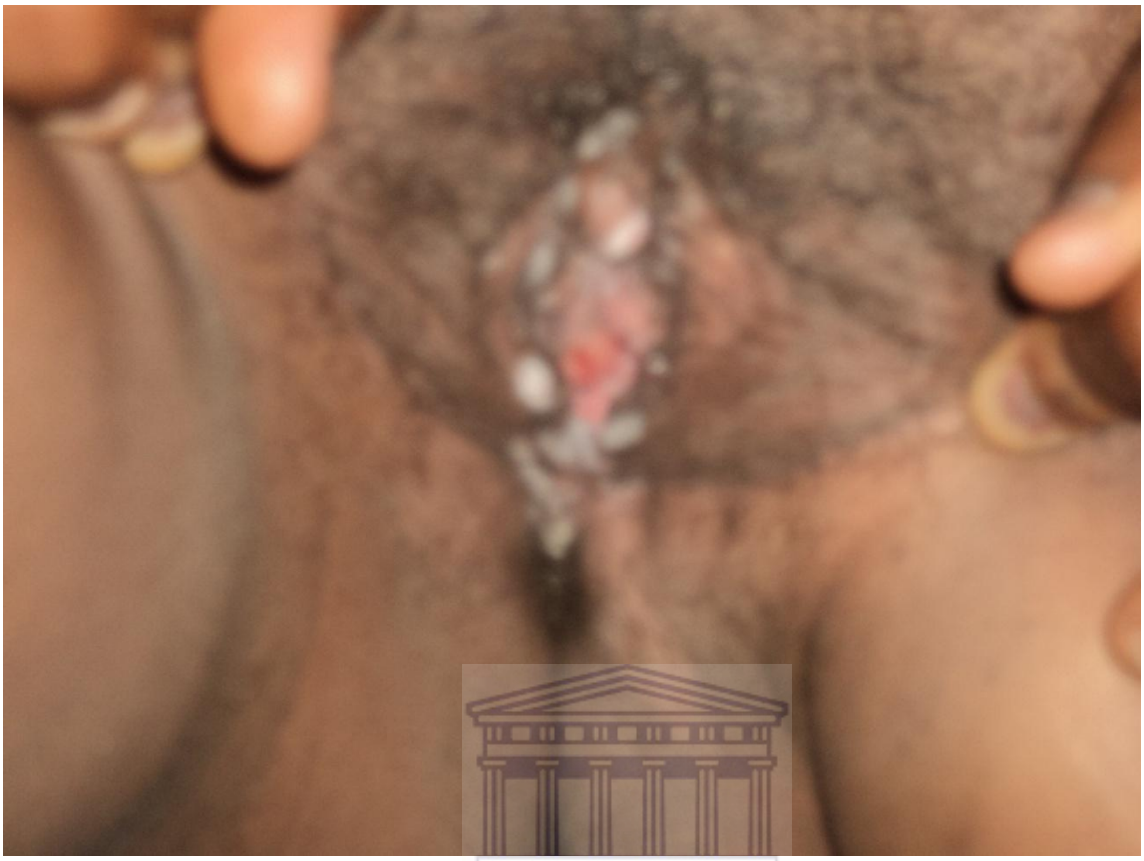

Fig. v: Genital warts co-existing with vaginal candidiasis in a 28 year old woman on HAART

APPENDIX 9

SAMPLE SIZE TABLE (The Research Advisors, 2006)

Required Sample Size								
	Confidence = 95%				**Confidence = 99%**			
Population Size	Margin of error				Margin of Error			
	5.0%	3.5%	2.5%	1.0%	5.0%	3.5%	2.5%	1.0%
10	10	10	10	10	10	10	10	10
20	19	20	20	20	19	20	20	20
30	28	29	29	30	29	29	30	30
50	44	47	48	50	47	48	49	50
75	63	69	72	74	67	71	73	75
100	80	89	94	99	87	93	96	99
150	108	126	137	148	122	135	142	149
200	132	160	177	196	154	174	186	198
250	152	190	215	244	182	211	229	246
300	169	217	251	291	207	246	270	295
400	146	265	318	384	250	309	348	391
500	217	306	377	475	285	365	421	485
600	234	340	432	565	315	416	490	579
700	248	370	481	653	341	462	554	672
800	260	396	526	739	363	503	615	763
1,000	278	440	606	906	399	575	727	943
1,200	291	474	674	1,067	427	636	827	1,119
1,500	306	515	759	1,297	460	712	959	1,376
2,000	322	563	869	1,655	498	808	1,141	1,785
2,500	333	597	952	1,984	524	879	1,288	2,173
3,500	346	641	1,068	2,565	558	977	1,510	2,890
5,000	357	678	1,176	3,288	586	1,066	1,734	3,842
7,500	365	710	1,275	4,211	610	1,147	1,960	5,165
10,000	370	727	1,332	4,899	622	1,193	2,098	6,239
25,000	378	760	1,448	6,939	646	1,285	2,399	9,972
50,000	381	772	1,491	8,056	655	1,318	2,520	12,455
75,000	382	776	1,506	8,514	658	1,330	2,563	13,583
100,000	383	778	1,513	8,762	659	1,336	2,585	14,227
250,000	384	782	1,527	9,248	662	1,347	2,626	15,555
500,000	384	783	1,532	9,423	663	1,350	2,640	16,055
1,000,000	384	783	1,534	9,512	663	1,352	2,647	16,317
2,500,000	384	783	1,536	9,567	663	1,353	2,651	16,478
10,000,000	384	784	1,536	9,594	663	1,354	2,653	16,560
100,000,000	384	784	1,537	9,603	663	1,354	2,654	16,584
300,000,000	384	784	1,537	9,603	663	1,354	2,654	16,586