

**An Overview of the Causes of Morbidity and
Mortality among HIV infected Older Adults at
Kenyatta National Hospital.**

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W64/80253/2012

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Declaration

I declare that this is my original work and has not, to the best of my knowledge, been presented elsewhere.

This thesis is submitted in partial fulfillment of the award of Master of Science Degree in Tropical and Infectious Diseases at the University of Nairobi.

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Acknowledgement

I would like to express my deepest gratitude to the people who facilitated this project.

Mr. Kipkemei and Mr. Kariuki of the Records' Department, Kenyatta National Hospital, who made access to data needed effortless. Mrs. Mary Wambui of the Comprehensive Care Center - IT department, who was exceptional in her willingness to help; giving both skill and time to prepare much needed data from the CCC data-base.

I am especially thankful to my supervisors Dr. Joshua Kimani and Dr. Marianne Mureithi whose expert guidance and valuable input helped shape this project from a very rough draft into a complete work.

To my family, friends and classmates, the moral support has been overwhelming; I am thankful.

It has been a privilege

Abbreviations

ABC	Abacavir
AIDS	Acquired Immune deficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
ATV/r	Atazanavir / Ritonavir
AZT	Zidovudine
CCC	Comprehensive Care Clinic
CKD	Chronic Kidney Disease
CMV	Cytomegalovirus
DNA	Deoxyribonucleic acid
D4T	Stavudine
EFV	Efavirenz
ERC	Ethics Review Committee
ESRD	End Stage Renal Disease
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus

HIVAN	Human Immunodeficiency Virus Associated Nephropathy
ICR	Institute of Clinical Research
IL-6	Interleukin 6
KAIS	Kenya AIDS Indicator Survey
KAVI	Kenya AIDS Vaccine Initiative
KNH	Kenyatta National Hospital
LMIC	Low and Middle Income Countries
LPV/r	Lopinavir/ Ritonavir
MDS	Minimum Data Set
MSM	Men who have Sex with Men
NNRTI	Non- Nucleoside Reverse Transcriptase Inhibitors
NRTI	Nucleoside Reverse Transcriptase Inhibitors
NVP	Nevirapine
PCP	Pneumocystis carinii Pneumonia
PEP	Post- exposure prophylaxis
P.I	Protease Inhibitors
PLHIV	People/Persons Living with Human Immunodeficiency Virus

RNA	Ribonucleic acid
TDF	Tenofovir
TNF α	Tumor Necrosis Factor alpha
UNITID	University of Nairobi Institute of Tropical and Infectious Disease
UON	University of Nairobi
3TC	Lamivudine

Abstract

Back-ground

The HIV epidemic is aging due to increased life expectancy among those on Highly Active Antiretroviral Therapy (HAART) and a significant number of poorly reported new infections in the older adult. Several studies have demonstrated a drastic decline in AIDS morbidity and mortality and an increase in non AIDS morbidity and mortality among HIV infected persons. Aging complicates HIV infection as it is accompanied by physiological changes that affect immunity, metabolism and overall systemic well-being. This has an impact on response to HAART, drug toxicity and comorbidity. Moreover, older adults are more likely to be diagnosed in the late stages of HIV and therefore have poorer outcomes.

Study objective

To determine the causes of morbidity and mortality among HIV infected older adults who were enrolled and accessed services at the Kenyatta National Hospital (KNH) from 1st June 2011 to 31st May 2013.

Methodology

A cross-sectional retrospective study was carried out at KNH. Data from 389 randomly selected adults aged 50 years and older as of 2011, who were served at the Comprehensive Care Clinic (CCC) over the two year period, was analyzed. Data was derived from patient files on socio-demographics, medications, HIV parameters, morbidity and mortality using a standardized data abstraction tool.

Results

During the two year study period, 16.5% of persons who accessed services at the center were older adults. In total 389 participants were included in the study; the mean age of participants was 58.5 years with a male to female ratio of 0.96:1. Overall, 74% of all subjects had morbidity other than HIV and the prevalence of late stage HIV disease among those diagnosed within the study period was 50%. The commonest non-infectious conditions were hypertension, diabetes and chronic kidney disease with prevalence of 35.5%, 11.6% and 10.8% respectively whereas the leading causes of infectious conditions were pulmonary tuberculosis (9%) and pneumonia (3.6%). Non-AIDS defining and AIDS defining cancers had comparable prevalence of 2.3% and 2.6% in this cohort. Due to these comorbidities, the prevalence of polypharmacy was 70% though drug interactions were documented in only 0.3% of the population. Adverse drug reactions occurred in 22% of all subjects and accounted for 9% of all admissions. The admissions due to infectious conditions and non-infectious conditions were comparable with prevalence of 53.6% and 51.5% respectively of all admissions. 6 out of the 8 deaths reported within the study were due to AIDS.

Conclusion

This study confirms that HIV infected older adults in our setting are facing a double burden of comorbidities; age related pathology and HIV associated complications. In light of the increasing proportion of HIV infected older adults, more needs to be done in terms of research. This information will be crucial in managing and scaling up programs targeting this unique subset of those living with HIV.

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1.0 Background

The Human Immunodeficiency Virus (HIV) remains a global health concern even as the epidemic enters its fourth decade. By 2013 it had claimed more than 39 million lives and it is estimated that globally, there are between 32- 38 million persons living with HIV (PLHIV); 71% of these PLHIV live in sub-Saharan Africa (WHO 2014).

The HIV epidemic has been described as a complex ‘long wave event’ with effects of the epidemic predicted to gradually emerge through the decades (Barnett, 2006). The epidemic has been continuously evolving; initially diagnosed among men who have sex with men (MSM) in 1981 in North America and Western Europe, it has since spread globally; by 2012, nine countries in sub-Saharan Africa, had one third of the world’s PLHIV (De Cock *et al*, 2012). In addition, contrary to the initial homosexual burden of disease, by 1993, AIDS transmission due to heterosexual spread increased by 130% and that due to homosexual transmission decreased by 20% (Quinn TC, 1995).

In Kenya, HIV was first diagnosed in 1984 among female sex workers and their clients. Today the epidemic is described as generalized, with relatively low risk behavior carrying a significant risk of transmission; 44% of all new infections in Kenya take place in heterosexual relationships in union or with regular partners, (NACC and NASCOP, 2012). The HIV prevalence in Kenya is 5.6% among persons aged between 15 and 64 years, with a total of 1.6 million people living with HIV (KAIS 2012, Kenya HIV prevention revolution roadmap, 2013).

In keeping with the predicted evolution, it is becoming increasingly evident that the HIV epidemic is aging with UNAIDS’ estimating the prevalence of older adults being between one quarter and one third of that of persons aged between 15 and 49 years (WHO 2009).

This aging phenomenon has been attributed to several factors; the success of Antiretroviral therapy (ART) with subsequent increase in life expectancy, the reduction in incidence among younger adults and the demonstrated risky behavior among older adults similar to that of the younger population (Samji *et al*, 2013, UNAIDS 2012, UNAIDS 2013). However, little research has been carried out on HIV infected older persons in Africa to date.

The aging HIV epidemic presents new challenges in terms of care and prevention strategies. HIV infected older adults are more likely to be diagnosed late in disease, with most of their symptoms being attributed to aging (Longo *et al* 2008, Larceda *et al*, 2008). In addition, older persons living with HIV have faster disease progression with shorter life expectancy than their younger counterparts (WHO 2009). Older adults have less than optimal response to ARV drugs due to immune senescence, with an increased likelihood of AIDS morbidity and mortality (Grabar *et al*, 2004). Moreover, due to the aging process, older PLHIV are likely to suffer from other diseases in addition to HIV which predictably leads to polypharmacy with possible drug interactions as well as augmented pathology (Marzolini *et al*, 2011). Studies done in developed countries demonstrate an increasing burden of non-AIDS morbidity and mortality among PLHIV of all ages (Krentz HB *et al*, 2005, Deek *et al*, 2009). Due to their altered physiology and immunity as well as age associated comorbidities, HIV infected older adults constitute a unique group in the epidemic that requires special attention. Numerous studies have been carried out in HIV; majority focus on adults aged 15-49 years and there is limited a number of studies carried out on HIV infected older adults, more so in our set up.

The definition of an older adult is variable and one that has sparked a lot of debate. HelpAge International views adults aged older than 55 in developing countries and those aged 60-65 years in developed countries as older adults (HelpAge International, 2008). WHO defines the older

adult as one who is 65years or older. However in its Minimum data Set (MDS) project and Study on Global Ageing and Adult health (SAGE), the proposed working definition for an older person in Africa was selected as 50 years and older; this was based on the fact that chronological age alone was not applicable in Africa and required the use of functional and social definitions as well, (WHO). Most studies done in HIV as well as Demographic and Health Surveys put emphasis on persons aged between 15-49 years. In this study, due to the proposed study area (a developing country) as well as in the interest of being comprehensive, the definition of an older adult is considered 50 years and older.

This study focused on HIV infected adults 50 years and older at Kenyatta National Hospital (KNH); it outlined the causes of morbidity and mortality in these individuals over a two year period, from 1st June 2011 to 31st May 2013. The retrospective study was carried out as an exploratory study to uncover the local patterns of disease in this subset of people living with HIV.

2.0 Literature review

2.1 Introduction

HIV belongs to the family *Retroviridae*, genus *Lentivirus*. It is an enveloped virus that contains a retrovirus genome of two identical copies of single stranded RNA molecules. HIV shows tropism towards cells of the immune system that express the CD4 receptor and the co-receptors CCR5 and/or CXCR4. Following infection, the viral genome is then integrated into the host cell DNA facilitating viral replication, (Manson's Tropical Diseases, 2008)

Destruction of CD4 cells leads to immune dysregulation and suppression with the subsequent immunosuppressive clinical presentation characteristic of Acquired Immunodeficiency Syndrome (AIDS).

Transmission

Today the most common mode of spread is sexual transmission; other modes of transmission include: - perinatal transmission from an infected mother to her child, as well as by infected blood through blood transfusion and use of contaminated needles and surgical instruments, (Manson's Tropical Diseases, 2008, MOTS 2008).

HIV Infection

Clinically, HIV is associated with acute and chronic phases. The acute phase of infection lasts 7-14 days during which there is rapid decline of CD4 cells and high viremia. Flu- like symptoms of varying severity may also occur in this period. Subsequently, the body mounts an immune response that leads to a clinically asymptomatic phase. Despite this clinical reprieve, HIV continues to replicate counter-acting anti-viral immunity with resultant chronic inflammation.

The HIV virus escapes the immune system by persistence of the in sanctuary sites, low expression of HIV antigens, and the high frequency of mutation within the viral genome (Manson's Tropical Diseases, 2008).

During the asymptomatic period, HIV continues to cause pathology with progressive loss of CD4-T lymphocytes and the chronic activation of immune cells (Deek 2011, Desai, 2010). Further disease progression occurs when the host immunity fails to contain HIV replication; CD4-T cell numbers drop giving rise to opportunistic infections. In the absence of treatment, WHO/UNAIDS estimates the mean time from infection to AIDS related death at 11 years. However, disease progression is extremely variable ranging from 3-20 years; rapid progressors develop AIDS in 3-5 years, whereas long-term non-progressors or 'elite controllers' may remain asymptomatic for 10-20 years (Poropatich & Sullivan, 2011).

Treatment of HIV

The treatment of HIV infected individuals involves the use of Antiretroviral drugs (ARV). There are currently six classes of ARVs: Nucleoside reverse transcriptase inhibitors (NRTI), Non-nucleoside reverse transcriptase inhibitors (NNRTI), Protease Inhibitors (PI), Entry inhibitors, Integrase Inhibitors and Maturation inhibitors. In Kenya, guidelines for first and second line therapies include the use of NRTIs, NNRTIs and PIs. Third line therapy is not readily available and includes the use of Integrase Inhibitors and new generation NNRTIs and PIs following drug resistance testing, (Ministry of Health, 2014).

Due to the high adaptability of the HIV virus which leads to the rapid development of resistance to mono-therapy, the current protocol entails the use of 3 different ARVs from 2 different classes. Current first-line therapy in Kenya involves the use of 2 NRTIs and 1 NNRTI; the

recommended first line regimen is Tenofovir (TDF), Lamivudine (3TC) and Efavirenz (EFV), unless there is pre-existing renal disease, in which case, TDF is replaced with Abacavir (ABC). An alternative first line is the replacement of TDF with Zidovudine (AZT), or EFV with Nevirapine (NVP) or substitution in both classes (Ministry of Health 2014). In 2010, WHO recommended the phasing out of Stavudine due its severe and long term side-effects. Since then, Stavudine use has been gradually phased out; in Kenya almost 30% of all persons on ART were on Stavudine in 2011, a sharp decline from 70% in 2010 (WHO, 2013).

Second line therapy in Kenya involves the use of two NRTI (TDF, AZT or ABC with 3TC) and a PI. PIs available in Kenya include Ritonavir boosted Atazanavir (ATV/r) or Ritonavir boosted Lopinavir (LPV/r), (MOH, 2014). It is estimated that 6% of all persons on first line therapy in Sub-Saharan Africa, will switch to second line therapy in any given year (UNAIDS, 2013). Virologic failure has been attributed to intrinsic drug resistance, evolution of acquired mutation, duration of treatment and poor adherence (Ajose *et al*, 2012). Protease Inhibitors have a high genetic barrier to resistance and treatment failure is often due to non-adherence (Fernandes *et al*, 2009, Van zyl G *et al*, 2011). In a South African study the prevalence of mutations for NRTI, NNRTI and PI was reported to be 54%, 29% and 6% respectively (El-Khatib *et al*, 2010). Virologic failure on second line therapy was associated with duration of exposure to previous drug regimens in addition to poor adherence (Ajose O *et al* 2012).

The institution of ART has been progressively revised; currently WHO recommends ART for all HIV positive adults with CD4 counts of 500 cells/mm³ or less. The previous WHO recommendation that was widely adopted in 2010 was set at 350 cells/mm³ or less, (WHO, 2013). This new guideline has been adopted in Kenya, (Ministry of Health, 2014).

HIV in the Post-ART era

In an unparalleled move in 2003, the Director General of the World Health Organization (WHO), declared the lack of access to ART a global health emergency. This pivotal action changed the course of the HIV epidemic by giving increasing access to ART (WHO, 2004).

In 2012, 9.7 million PLHIV received ART in LMIC; however, an estimated 19 million persons eligible for ART under the new guidelines had no access to ART (WHO, 2013). In Kenya, 84.5% of adults eligible for ART under the old guidelines received it, nonetheless, it is estimated that under the new WHO 2013 guidelines adopted only 45.9% of those eligible received it (KAIS, 2012, Ministry of Health, 2014).

With the advent of and wide-spread accessibility of ART, HIV has become a chronic rather than terminal disease and with timely institution of therapy, the life expectancy of PLHIV is fast approaching that of the general population. A study done encompassing data from the United States and Canada showed that a HIV positive adult aged 20 years on ART is expected to live into their early 70s (Samji *et al*, 2013). As an indirect measure of the impact of ART, a study done in rural KwaZulu- Natal, South Africa showed an increase in life expectancy by 11.3 years, from 49.2 years to 60.5 years in the general population which coincided with the introduction of ART in the Public Sector (Bor *et al*, 2013).

2.2 Epidemiology

Few studies have been carried out on the epidemiology of HIV in the older adult. In sub-Saharan Africa, studies done focused on how older adults were affected by HIV/ AIDS and not HIV infection in the same.

According to UNAIDS, there were 3.6 million older adults (50 years and older), living with HIV globally, with 2.9 million living in Sub-Saharan Africa in 2012. Furthermore, it is estimated that 10% of all PLHIV in LMIC are 50 years and older with an estimated 100,000 new infections annually (UNAIDS 2013).

In another study that sought to compare the 2013 UNAIDS estimates of prevalence in those older than 50 years, with house-hold surveys, there were 4.2 million PLHIV aged 50 years and older (twice as high as the figure in 1995) in 2013. The study found that both indicate steadily increasing prevalence of PLHIV aged 50 years and older (Mahy *et al*, 2014).

A study done by Negin *et al* in 2010 used existing data to extrapolate the prevalence of HIV infection in the older adult. The results estimated that there were 3 million persons aged 50 years and older who were living with HIV in sub-Saharan Africa (14.3% of PLHIV older than 15 years). In Kenya, the same study used data from the Kenya AIDS Indicator Survey (KAIS) 2007; the results showed that the prevalence of HIV in males and females aged 50-54 was 8.3% and 7.5%, and those 55-59 was 2.3% and 4.7% whereas those aged 60-64 was 3.4% and 1.7% respectively. The overall prevalence of HIV in persons aged 50 and over in Kenya was estimated to be 5.6% and it is projected that these figures will continue to rise over the next decades (Negin *et al*, 2010).

The aging of the HIV epidemic has been attributed to several factors. The success of ART has led to prolongation of life and therefore an increase in prevalence of older PLHIV (Samji *et al*, 2013, Bor *et al*, 2013). It is also postulated that the reduction in incidence among younger adults is causing a shift disease burden to older adults. Furthermore, contrary to ageist views, it has been found that older adults often engage in risky behavior that is comparable to younger persons (UNAIDS, 2013). In Malawi, a study done to compare the sexual behavior and HIV infections of persons aged 15-49 years and that of persons aged older than 50 years found that of the men and women aged 65 years and older, 73.8 % and 26.7% had had sex in the previous year respectively. In addition, men were more likely to have more than one partner. The HIV prevalence in men aged 50-64 was 8.9% compared with 4.1% for those aged 15-49 (Freeman *et al*, 2012).

2.3 The Aging process and pathology

Aging is defined as the decline and deterioration of functional properties at the cellular, tissue and organ level, (Fedarko, 2011). It is characterized by loss of homeostasis and decreased adaptability to internal and external stress and increased susceptibility to morbidity and mortality (Sedivy *et al*, 2013). Immunosenescence is defined as impairment in immunity as a result of age associated changes in the function of a variety of cells; it is a phenomenon of reduced function involving changes in both innate and adaptive immunity (Pawelec *et al* 2010).

2.4 Immune-senescence in the older adult

Cellular senescence was first described by Leonard Hayflick in 1965 while observing a cell culture and refers to essentially irreversible arrest of cell proliferation (growth) that occurs when cells experience potentially oncogenic stress. Senescent cells exhibit changes in chromatinization and gene expression and produce pro-inflammatory cytokines (Campisi, 2013). These secretions may be beneficial (tumor suppression and tissue repair) or harmful (local and systemic inflammation). Transitory presence of these cells is beneficial whereas chronic persistence is considered harmful; senescent cells accumulate with age and are considered to be key in the aging process and age related pathology (Rodier & Campisi, 2011). Senescence of the innate immune system leads to increased production of pro-inflammatory cytokines which promote age associated disease (Aw D *et al*, 2007). T lymphocytes also undergo age related decline in function; this is attributed to involution of the thymus centrally and has been associated with Cytomegalovirus (CMV) infection peripherally (Pawelec *et al*, 2010).

2.5 HIV and Immunosenescence

ART has had impressive success in improving health outcomes and quality of life among PLHIV, however, it is increasingly evident that it does not completely restore health; HIV infected persons on ART are at an increased risk of non-AIDS morbidity (Hasse *et al*, 2011). PLHIV undergo accelerated immunological aging; these changes are more pronounced in persons with low CD4+ counts with subjects demonstrating an increased risk of non-AIDS related morbidity (Deek, 2011). Immune activation is proposed to be the leading cause of non-AIDS morbidity in HIV and there is a strong association between certain inflammatory markers and morbidity and mortality; these include Interleukin 6 (IL-6) and Tumor necrosis factor alpha

(TNF α) (Deek 2011). The impact of natural age-related senescence and accelerated senescence due to HIV infection in older HIV infected adults is still a blind-spot in research.

2.6 HIV and Aging

The interaction between HIV infection, HIV treatment, aging and co-morbidity is likely to be multifarious and the effects additive.

The chronicity of HIV infection and related co-infections that accompany it, leads to constant immune stimulation with chronic inflammation. Inflammation is the hall-mark of age associated co-morbidities. This leads to accelerated aging and immune senescence in HIV disease (Desai *et al*, 2010)

A prospective study done in 2004 in France with a total of 3015 patients of which 401 were 50 years and older, explored the immunologic and clinical response to HAART in patients over 50 years of age. The results revealed that though older persons had satisfactory virological response to HAART, the immune response was less than optimal with slower CD4 cell reconstitution and higher incidence of opportunistic infections (Grabar *et al*, 2004). This finding was replicated in a multi-cohort collaboration encompassing 33 European cohorts with a total of 49,921 ART naïve patients between 1998 and 2008 (COHERE study group *et al*, 2008).

Consequently, it is evident from these findings that older persons require some vigilance in terms of early diagnosis, timely institution of treatment and follow-up.

2.7 HAART in the older HIV infected Adults

Aging is associated with changes in function and composition of the human body. These changes are variable and require proper drug selection and dose adjustment for older individuals. Due to the decline in renal drug excretion, the elderly are often managed as renally insufficient patients. In addition, metabolic clearance of the liver is often reduced with subsequent increased risk of drug accumulation and toxicity. Older persons have less water and higher fat content than younger individuals; this greatly affects the distribution and half-lives of hydrophilic and lipophilic drugs respectively. Furthermore, there is a decline in function of homeostatic mechanisms which leads to stronger drug effects than in younger subjects (Turnheim *et al*, 2003).

ARVs are associated with well-known toxicities including, dyslipidemia, impaired glucose metabolism, hepatotoxicity, nephrotoxicity, lactic acidosis, neuropathy and pancreatitis, which are likely to be more pronounced in the older adult.

Currently there are no treatment protocols for the management of HIV in older adults. Most are put on standard regimens and have their treatment revised on subsequent follow-up based on outcome.

An important aspect of health in the older adult is the issue of Poly-pharmacy (the concomitant use of multiple medications), which increases the risk of drug-drug interactions and adverse drug events. A Swiss study, comparing HIV patients less than 50 years to those older than 50 years old, found that older patients were more likely to have more than one co-medication (82% compared to 61%), (Marzolini *et al*, 2011).

2.8 Co-morbidity in HIV

It is likely that older age, HIV and its treatment have additive, if not compounded effect on the health of an individual. Several studies on the prevalence of co-morbidities and their outcomes have been carried out to this effect, though relatively few have been done in sub-Saharan Africa.

In 2012, a South African study found that older persons were three times more likely to have co-morbidities than their younger counterparts, with a prevalence of 29.6%. (Negin *et al*, 2012). Similarly, a retrospective observational study carried out in Ontario Canada found that HIV positive person of all ages are more likely to suffer from co-morbidities and multi-morbidities when compared to age and sex matched HIV negative adults in the general population; the prevalence in multi-morbidity increased with age (Kendall *et al*, 2012).

Co-morbidity and multi-morbidity of non-AIDS diseases particularly diabetes and cardiovascular disease, non AIDS defining malignancies and osteoporosis become more important in the post-ART era and are likely to become increasingly significant in the coming years (Hasse *et al*, 2011). A systematic review of studies done on Embase and Medline, which examined studies done in 20 developing countries, revealed that over one third of persons living with HIV had cardiovascular disease, metabolic syndrome ranged from 13-28% but Diabetes was below 5% (Haregu *et al*, 2012).

The predisposition to comorbidities is multifactorial; the aging process, HIV treatment and many of the traditional risk factors such as genetic predisposition and life style. Indeed, a study done in Nigeria that compared cardiovascular risk factors among patients who were HAART naïve and those on HAART found a significant risk of dyslipidemia, hypertension and metabolic syndrome (Muhammad *et al*, 2013). In a large prospective study of cardiovascular risk with

antiretroviral therapy, which encompassed 23,468 subjects, found that HIV infected persons who exhibited multiple risk factors for cardiovascular disease (hypercholesterolemia, older age, male sex, Diabetes mellitus and prior cardiovascular disease), were associated with an increased risk of myocardial infarction. Moreover, NNRTIs and PIs used in combination or alone were found to alter the lipid profile and thus increasing the cardiovascular risk. In this study, the relative risk of an ischemic event was related to longer ART use, with a relative risk of 1.26 per additional year. The overall risk of cardiovascular disease was relatively low unless coupled with other risk factors (DAD study group, 2003).

Lipodystrophy in HIV, which has been linked to prolonged use of PIs and NRTIs, is associated with an increased risk of insulin resistance and metabolic syndrome (Hadigan *et al*, 2001). In another study involving 3,327 HIV infected adults in the U.S, Hepatitis C Virus (HCV) was found to be an important risk factor for Diabetes along with traditional risk factors (Butt *et al*, 2009).

The causes of Kidney disease in HIV are varied; ranging from HIV itself (HIV 1 associated nephropathy- HIVAN), acute and chronic adverse events of the drug as well as aging, chronic infections and lifestyle. In a study done in the U.S, which included 1241 participants on ART, 4.1% were found to have end-stage renal disease (ESRD) and 15% had chronic kidney Disease (CKD) (Wyatt *et al* 2007). Similarly, a study done in Western Kenya found an overall prevalence of 11.5% of renal disease and 4.8% prevalence of ESRD among HIV positive adults (Wools- Kaloustian K *et al*, 2007). A 12 year US study found that HIVAN was more common in African Americans and with advanced immune-suppression; HAART was associated with significant reduction in the incidence of HIVAN (Lucas *et al*, 2009). However, some of the common drugs used in the management of HIV are nephrotoxic e.g. ART (PIs and NNRTIs) and

antimicrobials drugs used in the treatment of Opportunistic infections (Aminoglycosides, Amphotericin B etc.).

Like all other diseases, Liver disease in HIV is multi-factorial. In Uganda, a study which recruited 8,715 HIV infected patients including those on HAART found prevalence of 0.8% for symptomatic liver disease with etiology ranging from infectious, drug toxicity and alcoholic (Ocama *et al*, 2008). Regimens that contain NRTIs and/or PIs have a higher likelihood of liver toxicity (Ogedegbe *et al*, 2003). Furthermore, hepatic toxicity of PIs is more pronounced in patients with either HCV and/or HBV co-infection with HIV (Sulkowski *et al*, 2000).

Loss of bone density begins at 35 years for both sexes and is part of the normal aging process; however it is accelerated in post-menopausal women due to decline in estrogen levels. The etiology of reduced bone mineral density, osteopenia and osteoporosis in the older HIV infected adults is as a result of an interplay between age, HIV and antiretroviral drugs. This places the subjects at an increased risk of bone fractures. Among pre-menopausal women it has been found that HIV positive women were more likely to have a lower bone density and osteoporosis than their HIV negative counterparts after 2.5 years of follow-up (Yin *et al*, 2011). This was replicated in a meta-analytical review of 37 cross-sectional studies on Medline and Embase on individuals older than 18 years. The results revealed that the prevalence of osteoporosis was 3 times greater in HIV infected individuals compared to uninfected persons. ART and in particular PI exposed had a higher prevalence of reduced Bone marrow density (Brown *et al*, 2006).

In this era of widespread ART use, AIDS defining cancers have declined drastically due to improved immunity; in contrast, there is a sharp increase in non-AIDS defining cancers in the same population. (Engels *et al*, 2006). A prospective study was carried out in Pittsburg that

followed 33420 HIV infected and 66840 HIV uninfected persons over 5.1 and 6.4 years respectively. The results showed a high risk of Non-AIDS defining cancers among HIV infected persons; an important finding was that these persons had lower CD4 cell counts than their HIV infected counterparts who were cancer free; nonetheless some non-AIDS defining cancers were unaffected by CD4 counts (Bedimo *et al*, 2007).

Data from studies reveal a decline in AIDS related deaths among adult PLHIV and an increase in the number of non-AIDS related morbidity and mortality cases reported (Collette *et al*, 2014, Krents *et al*, 2005). Moreover, HIV infected persons on HAART are still at an increased risk of death when compared with HIV negative persons; death is associated with HIV and non HIV associated risk factors (Obel *et al*, 2011). Despite the marked decline in AIDS related deaths in the general population, older people are still diagnosed late due to symptoms often being attributed to aging and not HIV. A study carried out in Italy found that among older adults, 67% were late testers compared to 32% of younger adults (Longo *et al*, 2008). Locally, in a study done in rural Nyanza in Kenya, AIDS was found to be a leading cause of death among older adults. The study utilized a community health worker administered verbal autopsy (Negin *et al*, 2012). Similarly, a study done in Brazil revealed that older persons were more likely to have delayed diagnosis and present with AIDS and AIDS defining illnesses. This age-group was also four times more likely to die (Larceda *et al*, 2008).

2.9 Rationale

Based on the current projections, the HIV epidemic is likely to continue aging, along with the general population. With the success of ART and increased access to treatment, HIV is becoming a chronic illness. This chronicity is likely to unearth a complex relationship between aging, HIV infection and non-AIDS related events. The older adult with HIV is more likely to have co-morbidity and HIV related disability in addition to the natural aging process. Anticipation of common causes of morbidity and mortality in the older HIV infected individuals would lead to high index of suspicion and assessment of common disease syndromes with subsequent early intervention. There is currently no treatment regimen targeting the older adult despite the fact that there are significant changes in physiology due to natural aging and co-morbidities that greatly alter drug pharmacokinetics and pharmacodynamics and the response to ARVs.

Furthermore, older persons are more likely to present late for HIV diagnosis and/or present late with AIDS defining illnesses. The impact on Public health and health planning is likely to be significant. Few studies have been done on older adults living with HIV in Sub-Saharan Africa and none has been carried out in Kenya; we hope that this study will shed some light on this very important aspect of the HIV epidemic in our setting.

2.10 Study Objectives

2.11 General objective

To determine the causes of morbidity and mortality among HIV infected older adults who were enrolled and accessed services at the Kenyatta National Hospital (KNH) from 1st June 2011 to 31st May 2013.

2.12 Specific objectives

- To describe the demographics and proportions of HIV infected persons aged 50 years and above at Kenyatta National Hospital.
- To assess the prevalence of chronic co-morbidity, multimorbidity (more than one chronic condition in addition to HIV) and polypharmacy in those aged older than 50 years.
- To determine the common medical diagnoses (AIDS and non-AIDS) among HIV infected older adults admitted at KNH
- To establish the common causes of mortality in those aged older than 50 years utilizing services at the site.

3.0 Methodology

3.1 Study design

This is a cross-sectional retrospective study that utilized medical records as a data source.

3.2 Study area

The study was carried out at the Comprehensive Care Center (CCC) and Records' Department (Clinic 19) at Kenyatta National hospital. It is a level 6 hospital providing the highest level of preventive and curative services including management of HIV patients and their complications.

The Comprehensive Care Center has enrolled 18,819 patients cumulatively over the years. It receives its patients as referrals from Voluntary Counseling and Testing Centers (VCT) located across the city and country, as well as referrals from other HIV management centers either for further management (as the CCC is also a referral center) or due to preference. In addition, patients newly diagnosed or found to be positive as in-patients at Kenyatta national Hospital are usually discharged through the CCC.

It provides services such as medical consultations, laboratory procedures, pharmacological services as well as psychological and nutritional counseling. When indicated, patients are referred for admission or to appropriate clinics at Kenyatta National Hospital.

3.3 Study population

The subjects were HIV infected individuals at the Kenyatta National Hospital seen at the Comprehensive Care Center.

3.4 Sample size calculation

The prevalence of co-morbidity, multi-morbidity and polypharmacy among older HIV positive adults is unknown in our set up. Prevalence is therefore assumed to be 50%.

$$n = \frac{Z^2 [P (1 - P)]}{(d)^2}$$

n- Minimum sample

Z- Constant 1.96 (95% confidence interval)

P-Population proportion with population of interest

Q- 1-P

d = Acceptable margin of error

Z = 1.96

P = 0.5

Q = 0.5

d = 0.05

$$n = \frac{(1.96)^2 \times 0.5(1-0.5)}{(0.05)^2}$$

n=384

The minimum sample size is 384

3.5 Sampling method

Multistage sampling was done; a list of persons who accessed services at the CCC between 1st June 2011 and 31st May 2013 was created. Those aged less than 15, those who were on Post exposure prophylaxis (PEP) as well as those who were considered ‘on transit’ (those who were seen once for the purposes of ARV refill but on follow up in other centers) were excluded. From this list, those who were 50 years and older as of 2011, were selected, blinding for mortality and sex, time of enrollment and duration of illness.

A list of 646 file numbers arranged chronologically from earliest to latest registered was created. Excel program was then used to randomize the numbers and the first five hundred files were selected.

To assess trends of proportions of older persons registered over the years, a list of all persons registered annually at the Comprehensive Care Center from 2005 to 2013 was created. These annual lists excluded those who were less than 15 years old, those on PEP and those ‘on transit’; this list was used as the denominator. From this initial list, those 50 years and older at

registration were identified; this second list was considered the numerator. Annual proportions were then carried out for each year. 2005 was selected as this was the earliest complete year in the data base at the time.

3.6 Sample selection

3.6.1 Inclusion criteria

HIV infected adults aged 50 years or older as of the year 2011, who were either:-

- Attending clinics at Kenyatta National Hospital
- Had been admitted at Kenyatta National Hospital
- Had died at Kenyatta National Hospital

3.6.2 Exclusion criteria

Those excluded from the study were:-

- Persons aged less than 50 years as at 2011
- HIV negative persons

3.7 Study materials

The study materials included stationary (the data collection sheets and pens), a computer and a flash disk.

3.8 Procedures

Sample selection was carried out at the CCC, using the CCC data-base; 500 participants were selected using multi-stage sampling. The final list of file numbers was delivered to the Records' department (Clinic 19), where the files were extracted by the staff. Of the 500 files selected, 88 were unavailable and 23 were found to belong to persons who did not fit the inclusion criteria; the final sample size was 389. Proportions of persons 50 years and older were calculated based on data from the CCC.

Participant files were examined and relevant data was collected and recorded in the Data collection sheets. No names or identifying data were documented and files were not carried out of the premises. At the end of the day, the data collection sheets were transported safely filed and stored under lock and key.

Bio-data and diagnosis as documented by the health care provider was recorded as was. In addition, adverse drug effects were documented only for drugs that warranted a change in medication. Dates were recorded for month and year in order to be able to analyze data in months. Where the year but not the month was provided, the month of June was used in order to achieve the requirements but also to introduce a systematic error that would not greatly bias the data. Confidentiality was maintained at all times.

3.9 Measures

The dependent variables recorded in this study included:-

- Treatment back-ground; duration since diagnosis, CD4 counts, World Health Organization (WHO) Clinic staging at diagnosis and enrolment, ART therapy, antibiotic and antifungal prophylaxis.
- Presence of comorbidity and multimorbidity
- Presence of polypharmacy
- Admissions and the diagnoses at admission
- Mortality and the causes of mortality

The independent variables in this study included: - Age, Sex, Marital status, level of education and residence.

3.10 Data collection instruments

Standardized data collection sheets were used to record data extracted from patient files. The study subjects were assigned numbers and no identifying data was recorded. The Data collection sheets were then filed and stored under lock and key.

3.11 Data management and analysis

Data was collected by the principle investigator, physically filed at the end of each day and stored under lock and key. Data was then coded and entered into the SPSS program in a password protected lap top and back up flash disk.

Data analysis was carried out by a qualified statistician using SPSS 21.

3.12 Ethical considerations

The study proposal was submitted to the Kenyatta National Hospital- University of Nairobi- Ethics Review Committee (KNH-UoN ERC) and approval received. Subsequently, a study registration certificate was obtained from the Kenyatta National hospital Research and Programs department.

There was minimum risk to the study subjects as data was collected from medical files. Confidentiality was highly prioritized; no files were carried out of the premises and the Data collection sheets were filed and stored under lock and key. There was no direct benefit to the participants; however this study is likely to fuel further studies which are likely to improve health-care for this population.

4.0 Results and analysis

In total, 500 participants were selected, via the randomization of a chronologically arranged list of 646 persons registered as older than 50 years old from 01/06/2011 to 31/05/2013. Of these, 23 were excluded based on age (50 years as of 2011), and 88 files could not be traced at the records department. The sample size ultimately comprised of 389 study participants.

Study participants

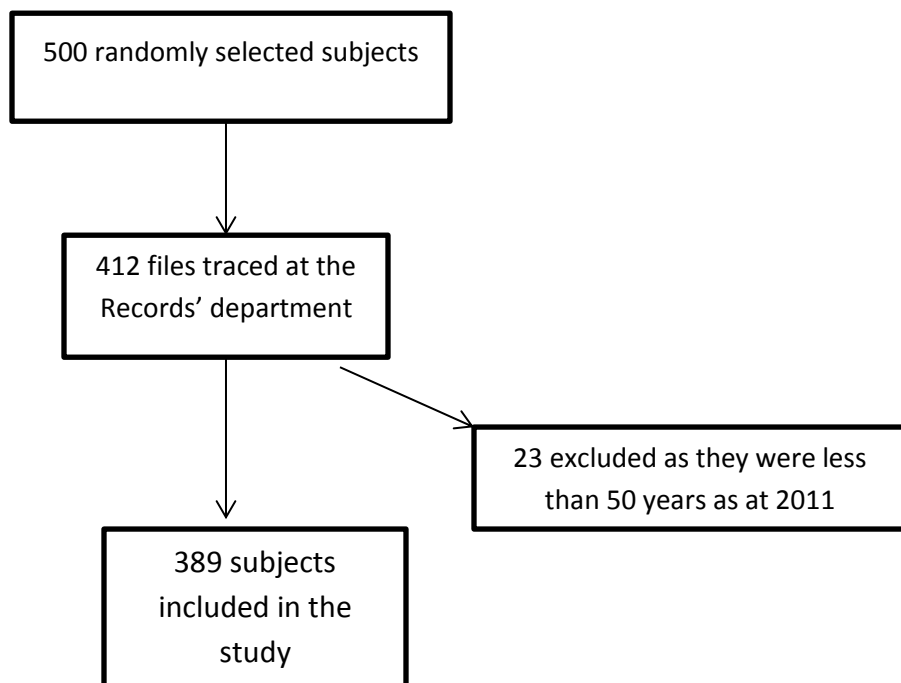


Figure 1- Study participants

4.1 The proportion of study participants 50 years and older at the CCC

The proportion of patients 50 years and older were assessed in two ways; the proportion of persons newly registered and the proportion of persons who received services at the CCC within the study period.

A list of all persons aged older than 15 years registered at the CCC per annum over a nine year period (from 2005 to 2013) was created. Persons on ‘transit’ and persons on PEP were excluded; subsequently, a list of those over 50 years at registration was extracted. The year 2005 was the earliest comprehensively recorded year in the CCC data- base.

Trends in the proportions of newly registered adults 50 years and older

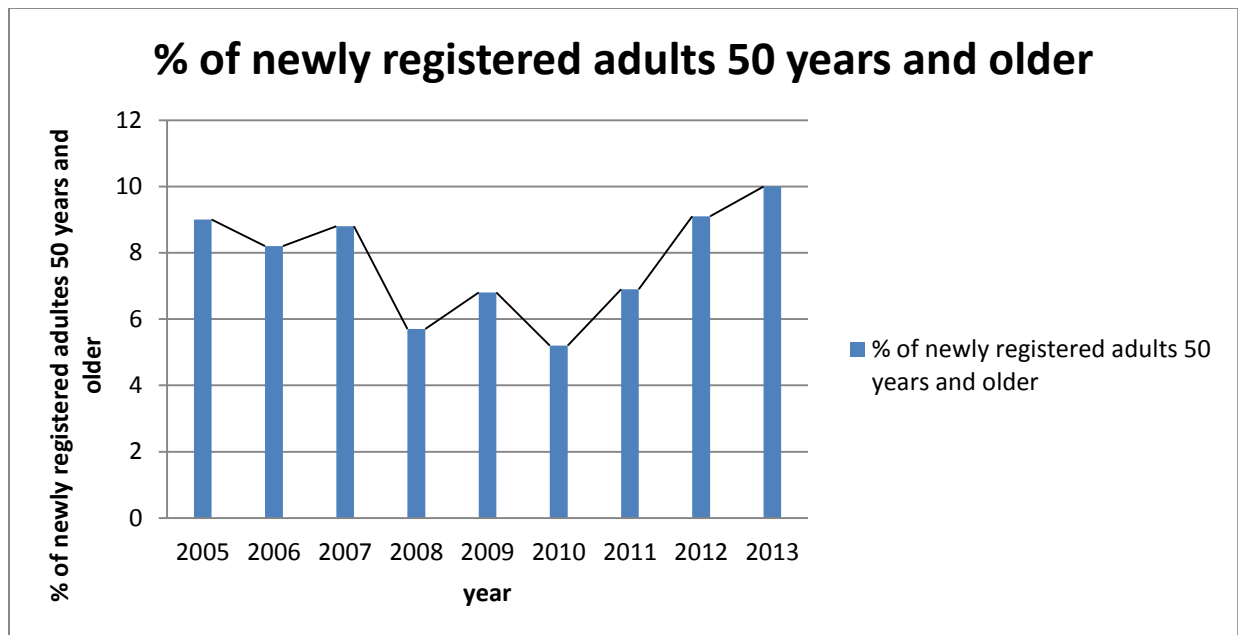


Figure 2- Trends in the proportions of newly registered adults 50 years and older

The trend shows an initial decline in the proportion of newly registered older adults, however, there has been a gradual increase in the last three years (2011 -2013). On average, older persons comprised 8.7% of newly registered persons at the CCC in the past 3 years.

Proportion of older persons seen at the CCC

Of the 3908 persons seen at the CCC within the study period, 16.5% (646) were older persons.

The mean age of participants was 58.5 years; the youngest participant was 50 years old and the oldest was 93 years old. When arranged categorically, majority of the subjects were between the ages of 55 and 59. There was near- equal representation of both sexes among the randomly selected subjects; with a male to female ratio of 0.96:1.

As expected, 65.8 % of the subjects were from Nairobi. In addition, a significant number (16.2%) were from neighboring counties/regions i.e. Machakos, Kajiado and Kiambu.

In total, 86.1% of participants had some formal education; only 4.6 % had no education. 9.3% had no information on their education recorded in their files. Of those with formal education, only 18.3% had attained higher learning. Majority of participants (89.7%), were of the Christian faith. 5.7% had no data on their religious affiliations recorded. 2.8% were of 'other' varied faiths not considered main-stream. Half of the subjects were married as at the time of registration; data on marital status as well as other bio-data was not routinely updated. Significantly, one third of selected participants were widowed. A little over one tenth (12.6%) were separated/ divorced, and 2.1% were single. Only 2.6% had data on their marital status missing from their files. 62.7% of subjects were either employed or self-employed; 28.3% were unemployed. 4.9% were retired and 4.1 had data missing from their files on occupation

4.2 Socio-demographic characteristics

Variable	Frequency (%)
Mean age in years (SD)	58.5 (5.8)
Min-Max	50-93
Categories, n (%)	
50-54	109 (28.0)
55-59	134 (34.4)
60-64	91 (23.4)
≥65	55 (14.1)
Sex	
Male	189 (48.6)
Female	200 (51.4)
Region	
Nairobi	256 (65.8)
Kiambu	34 (8.7)
Kajiado	15 (3.9)
Machakos	14 (3.6)
Other regions	31 (8.0)
Education	
None	18 (4.6)
Primary	139 (35.7)
Secondary	125 (32.1)
College/University	71 (18.3)
Missing	36 (9.3)
Religion	
Christian	349 (89.7)
Muslim	6 (1.5)
Hindu	1 (0.3)
Other	11 (2.8)
Missing	22 (5.7)
Marital status	
Single	8 (2.1)
Married	200 (51.4)
Separated/Divorced	49 (12.6)
Widowed	122 (31.4)
Missing	10 (2.6)
Occupation	
Employed	113 (29.0)
Retired	19 (4.9)
Unemployed	110 (28.3)
Self employed	131 (33.7)
Missing	16 (4.1)

Table 1- Socio- demographic characteristics

4.3 Treatment back-ground

The median duration of illness was calculated as duration from date of diagnosis to date of death, loss to follow-up or end of study i.e. 05/2013. The median duration of illness was 52 months (4.3 years) with the IQR of 21 months (1.8 years) to 88 months (7.3 years). The median CD4 count was 186 cells /mm³ with an IQR of 85-316 cells/mm³.

There was an association between gender and CD4 counts; females had relatively higher median CD4 counts than men at enrolment (where the p-value was <0.001).

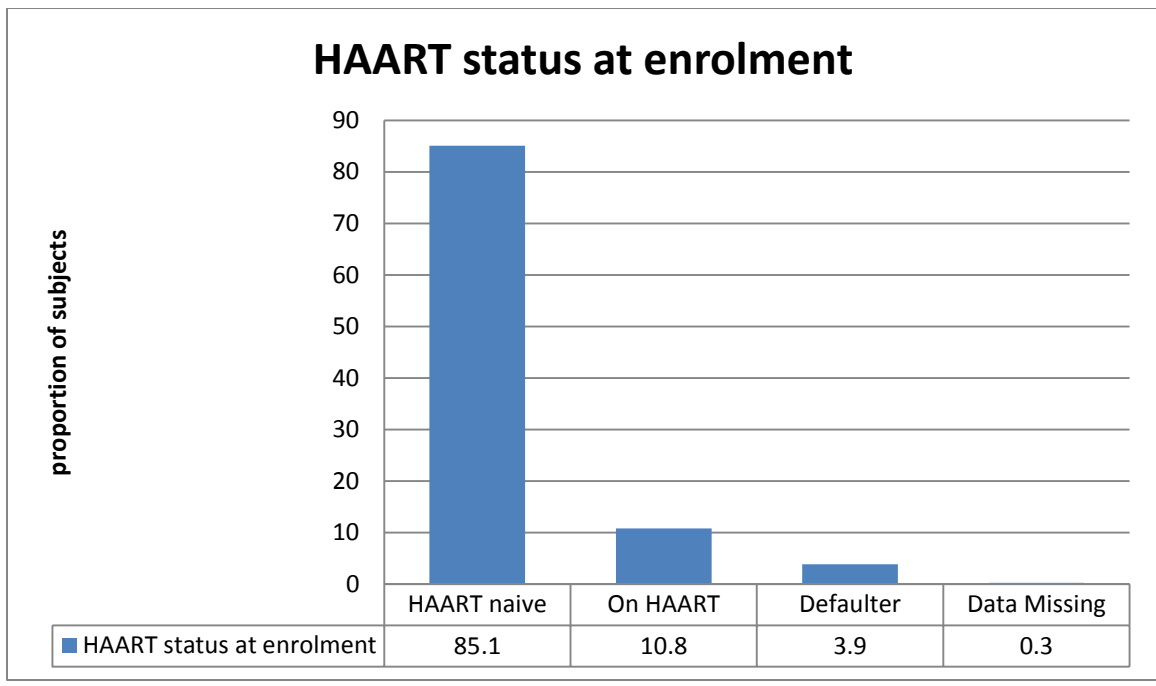


Figure 3- HAART status at enrolment

At enrolment 85% were HAART naïve 10% were already on HAART and defaulters comprised of 4% of subjects within the study. There was an association between higher CD4 count and use of HAART, even among defaulters. (p <0.001). Those with HAART exposure had generally

higher CD4 counts than those who were HAART naïve. Those on HAART, defaulters and those who were HAART naïve had CD4 counts of 314, 201 and 170 cells/mm³ respectively.

A comparison between HAART status and Clinical stage at enrolment demonstrated an association; the proportion of defaulters presenting with stage 3 and 4 disease was higher than that of those who were HAART naïve and on HAART

	On HAART	HAART Naïve	Defaulters	P value
Median CD4 at enrolment (IQR)	314 (206.0-544.0)	170 (79.0-301.0)	201 (47.0-334.0)	<0.001

Table 2- Association between HAART status and CD4 counts

	HAART Naïve	On HAART	Defaulters	P value
WHO stage at enrollment				
I	92 (28.1)	18 (45.0)	0	0.005
II	85 (26.0)	6 (15.0)	2 (14.3)	
III	112 (34.3)	9 (22.5)	10 (71.4)	
IV	38 (11.6)	7 (17.5)	2 (14.3)	

Table 3- Association between HAART status and Clinical staging

WHO clinical staging at diagnosis

Approximately one third of the subjects (108/389) were diagnosed within the two year study period. 50% presented with late stage disease (stage 3 and 4), with a little over one third having stage 3 conditions. There was no difference between the median CD4 counts and the WHO clinical staging at enrollment for those enrolled prior to the study period compared to those diagnosed within the same. There was evident similarity in the pattern of distribution with close to 50% presenting in the early stages of disease, and half presenting with late stage disease (stages 3 and 4)

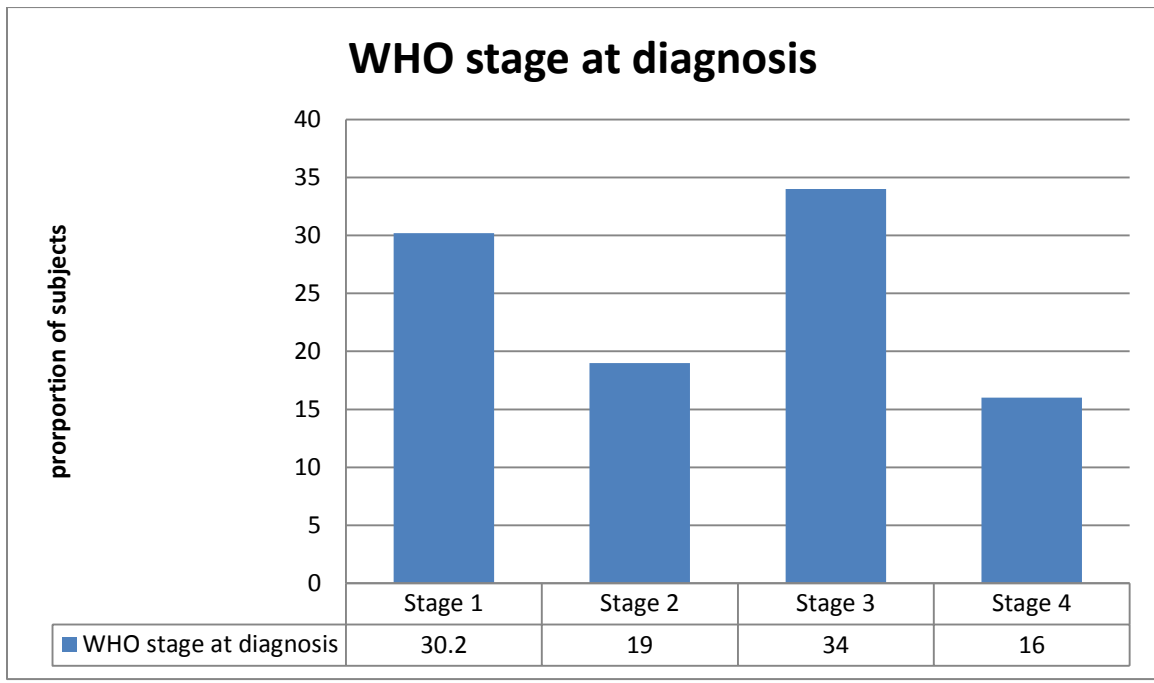


Figure 4- WHO stage at diagnosis

There was no demonstrated association between marital status and year of diagnosis with WHO clinical staging at diagnosis ($p = 0.115$ and $p=0.067$ respectively).

Variable	Time of HIV diagnosis		P value
	During study period	Prior to study period	
CD4 at enrolment	176 (67-362)	186 (87-314)	0.766
WHO stage at enrolment			0.121
I	32 (30.2)	67 (26.0)	
II	21 (19.8)	69 (26.7)	
III	36 (34.0)	99 (38.4)	
IV	17 (16.0)	23 (8.9)	

Table 4- Comparison of diagnosis within and prior to the study period

HAART status as at the study period

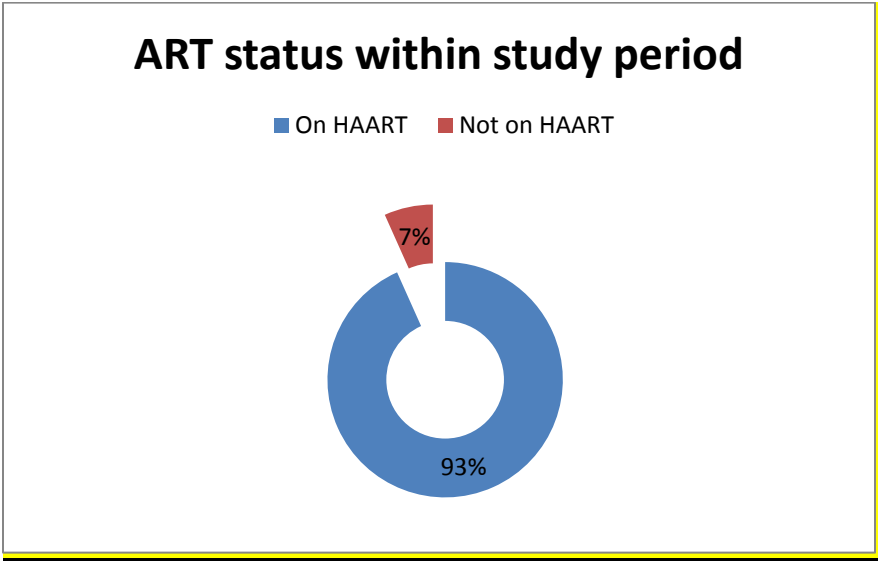


Figure 5- HAART status as at the end of the study

93% were on ART as at the end of the study period with one tenth of these on 2nd line regimens. There was an association between longer duration of illness and second line treatment (p value <0.001). Furthermore defaulter status appeared to be positively associated with being on second line therapy (p=0.027).

	Use of 2 nd line		P value
	Yes	No	
Median duration of illness (IQR)	98.5 (70.0-133.0)	51.0 (22.0-84.0)	<0.001

Table 5- Association between duration of illness and 2nd line therapy

	Defaulter		P value
	Yes (n=15)	No	
Use of 2 nd line			
Yes	4 (11.1)	32 (88.9)	0.027
No	11 (3.4)	315 (96.6)	

Table 6- association between defaulter status and 2nd line therapy

41% of patients had been on more than one first line regimen, of these, 38% had been on two regimens. There was an association between duration of treatment and number of first line regimens (<0.001). Median duration of treatment of those on one regimen was 29 months, while those who had been on two or three regimens had been on treatment for 79 and 105.5 months respectively.

The prevalence of ARV use i.e. Stavudine, Tenofovir, Zidovudine and Abacavir based regimens was calculated. The results showed that 70% and 32% of subjects had ever been on Tenofovir and Stavudine respectively.

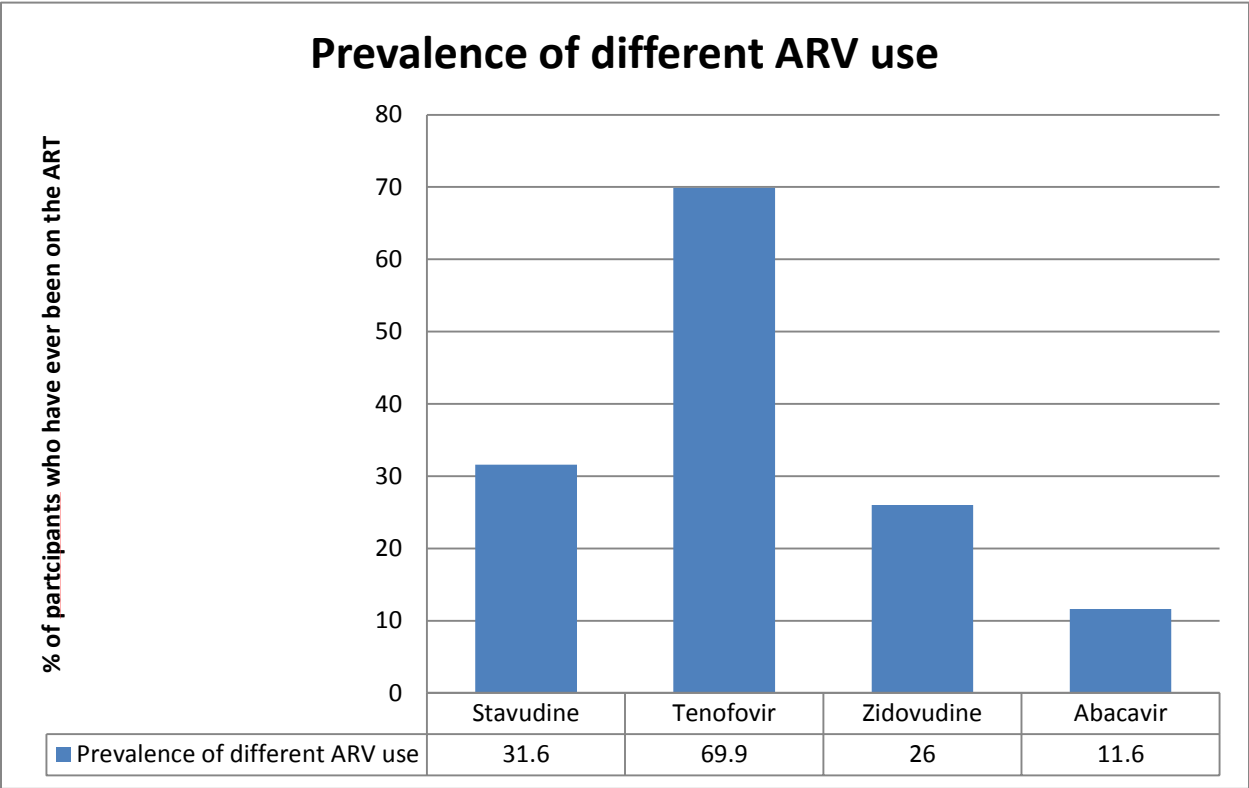


Figure 6- Prevalence of NRTI back-bone use

Prophylaxis

All subjects in the study were on PCP (Pneumocystis Carinii pneumonia) prophylaxis including those not on ART; 96% were on Cotrimoxazole and 4% were on Dapsone. 0.3% (1 subject) and 1.5% (6 subjects) were on Tuberculosis and antifungal prophylaxis respectively.

4.4 Comorbidity and multimorbidity

Comorbidity and multimorbidity

Total comorbidities	
0	102 (26.2)
1	133 (34.2)
2	89 (22.9)
3	47 (12.1)
4	12 (3.1)
5	5 (1.3)
6	1 (0.3)
Presence of other diseases	287 (73.8)
Comorbidity	133 (34.2)
Multi-morbidity	154 (39.6)

Table 7- Comorbidity and multimorbidity

The prevalence of other conditions other than HIV (co-morbidity and multi-morbidity) was high (74%). The prevalence of co-morbidity (one condition other than HIV) was 34.2% and that of multi-morbidity (more than one condition other than HIV) was 39.6%.

34% of patients had only one chronic condition in addition to HIV whereas 23.2% had two conditions. Only one person had 6 chronic conditions in addition to HIV.

There was an association between longer duration of HIV disease and presence of multi-morbidity. There was however no demonstrated association between age, sex, and duration of treatment and the presence of multi-morbidity.

Variable	Co-morbidity	Multi-morbidity	P value
Mean age (SD)	57.3 (5.2)	59.8 (6.3)	0.107
Sex			
Male	69 (49.6)	70 (50.4)	0.277
Female	64 (43.2)	84 (56.8)	
Median duration of illness (IQR)	47.5 (19.5-85.0)	59.0 (22.0-90.0)	0.049
Median duration of treatment (IQR)	45.5 (16.5-77.5)	53.5 (19.0-83.5)	0.527

Table 8- Association between age, sex, duration of illness and treatment with multimorbidity

Prevalence of comorbidities by systems

The most common systems with co-morbidity were the cardiovascular and nervous systems.

Non-AIDS defining cancers had an overall prevalence of 2.3%. Metabolic, Renal and skeletal diseases also contributed significantly to the overall morbidity.

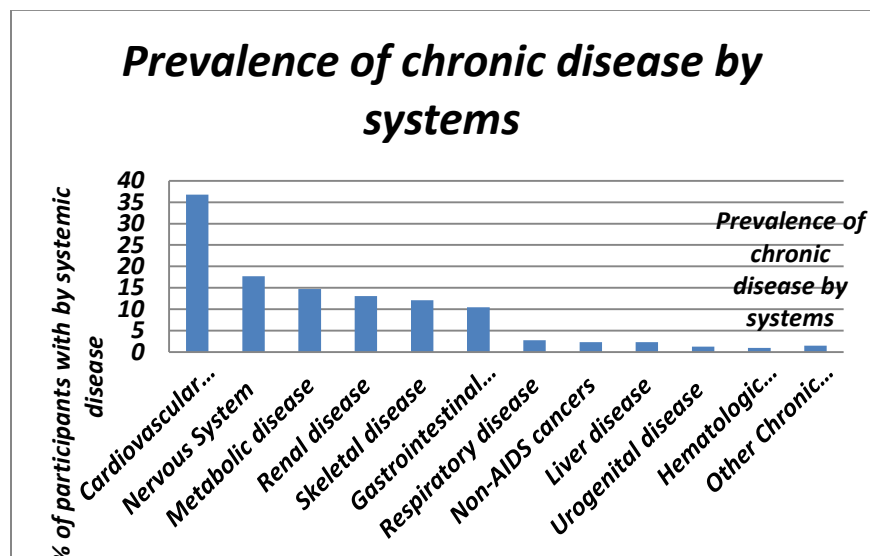


Figure 7- Prevalence of chronic disease by system

TOP 10 Chronic conditions

Hypertension had a considerably high prevalence at 35.5%. Diabetes ranked second with a prevalence of 11.6%. Significantly, renal insufficiency/ chronic kidney disease had a prevalence of 10.8%. There was incomplete documentation of the staging in chronic kidney disease therefore all degrees of insufficiency were recorded as chronic kidney disease.

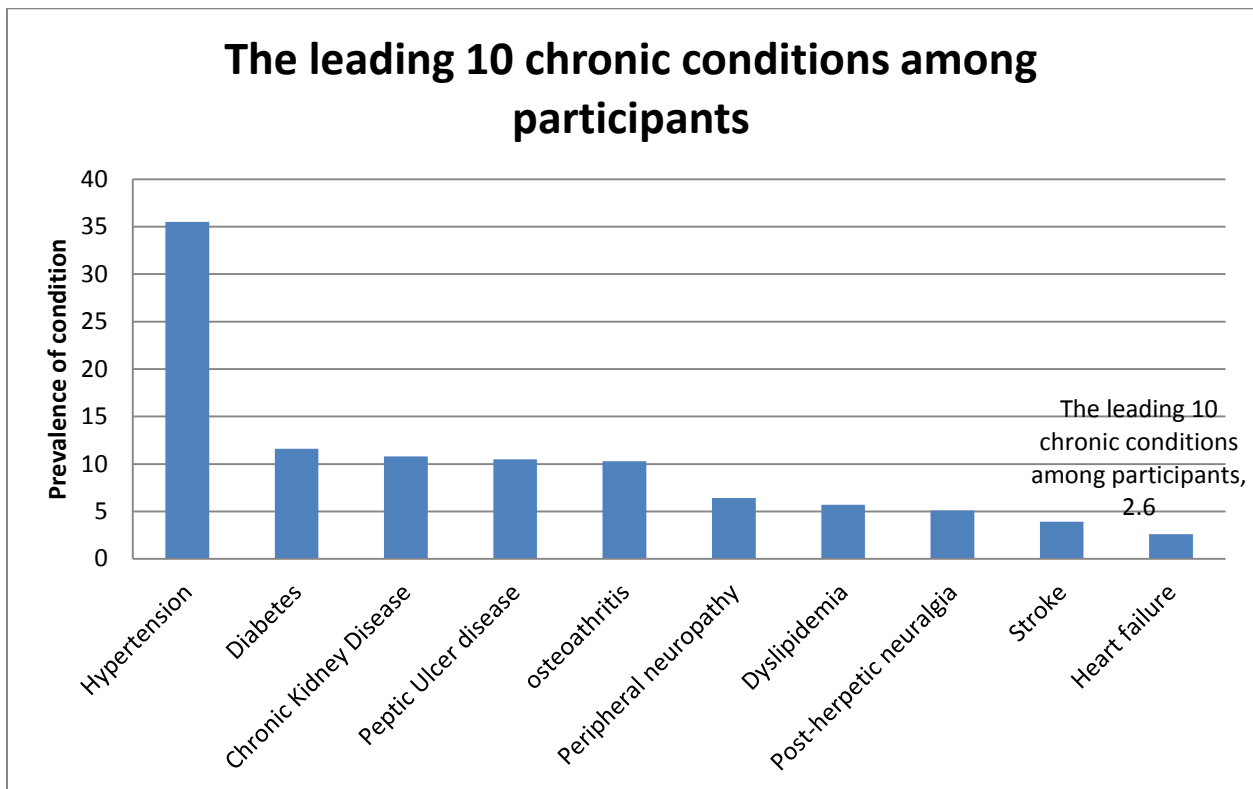


Figure 8- The 10 leading non-AIDS conditions among participants

4.5 Polypharmacy

70% of the subjects had polypharmacy, (the use of other drugs other than ARVs and PCP prophylaxis.) Enumeration of drugs was carried out as per drug class and not by pill burden or specific drug e.g. labeled 'anti-hypertensives' instead of 'Nifedipine, Hydrochlorothiazide', 'analgesics' instead of Diclofenac and so on and so forth.

Distribution of total number of drugs

36%, 22% and 10% of subjects were on one, two and three medications respectively.

Polypharmacy had no demonstrated association with age and sex.

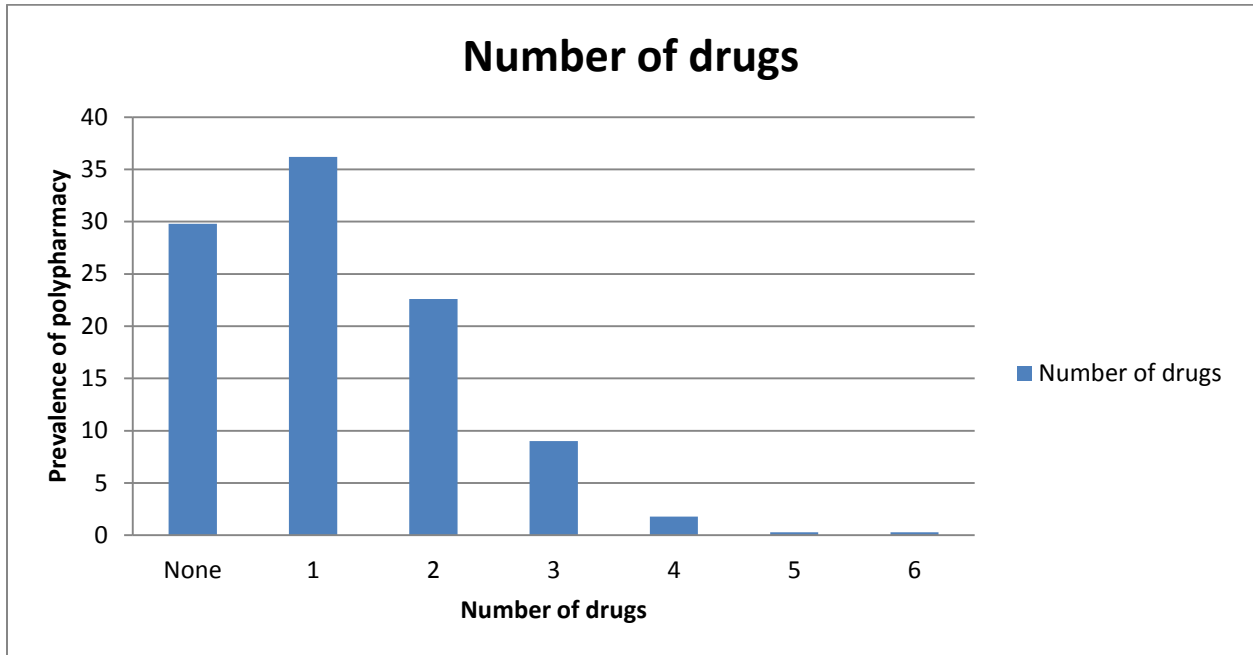


Figure 9- Distribution of total number of drugs

4.6 Adverse Drug Reactions

22% of subjects had had an adverse drug effect either before or during the study period. Adverse reactions caused by drugs taken prior to the study period were only recorded if their effects were still noted within the study period

Adverse drug effect description

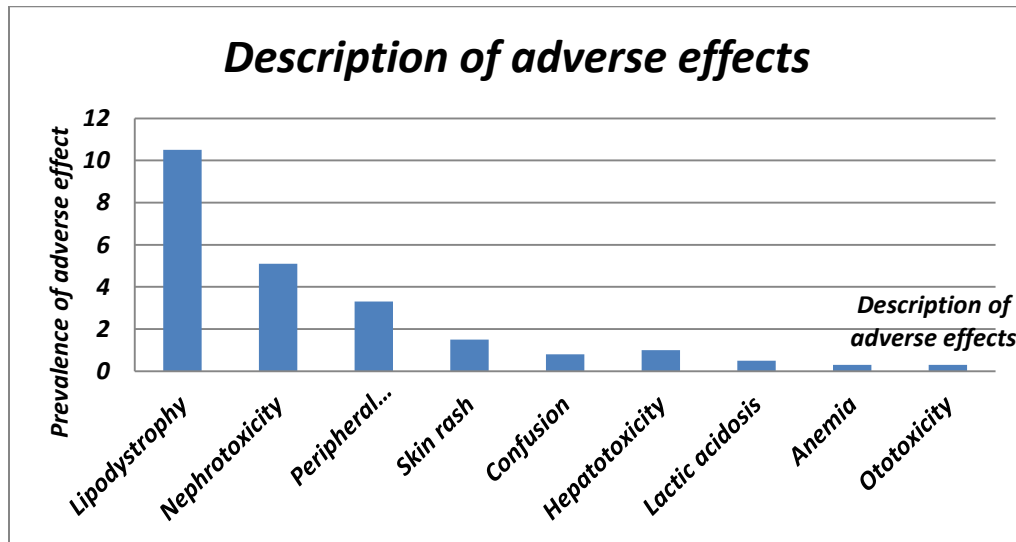


Figure 10- Description of adverse effects

The most common adverse effects were lipodystrophy, nephrotoxicity and peripheral neuropathy.

Drugs associated with common adverse effects

Drugs	N=389 n (%)	Adverse drug reaction		
		Prevalence	Description	n (%)
Stavudine	123 (31.6)	51 (41.5)	Lipodystrophy	37 (72.5)
			Peripheral neuropathy	12 (23.5)
			Lactic acidosis	2 (3.9)
Tenofovir	272 (69.9)	17 (6.3)	Nephrotoxicity	17 (100)
Zidovudine	101 (26.0)	4 (4.0)	Lipodystrophy	3 (75.0)
			Anaemia	1 (25.0)

Table 9- Drugs associated with common adverse effects

Stavudine was the leading cause of adverse drug effects with a prevalence of 41.5% among all who had ever used it; lipodystrophy accounted for 72% of its adverse effects. The prevalence of Tenofovir adverse effects was 6.3%; its only documented adverse effect was nephrotoxicity. Zidovudine adverse effects had a prevalence of 4% of which lipodystrophy was the most common. There was only one documented case of drug interaction, (0.3%).

4.7 HIV related Disease

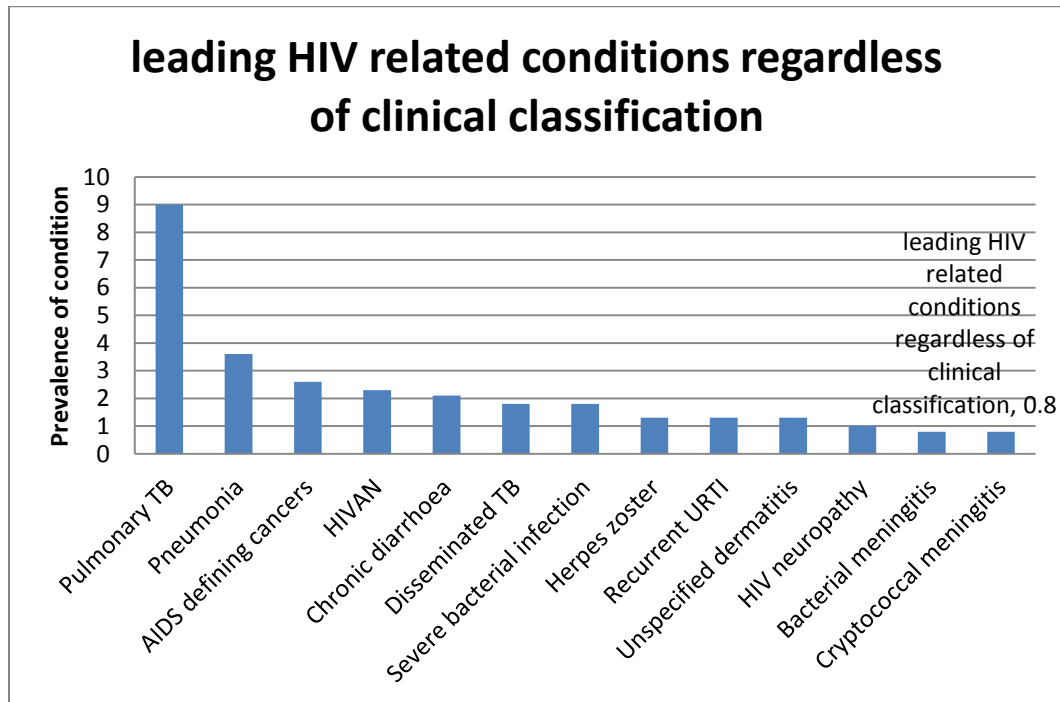


Figure 11- The leading AIDS related conditions

HIV related diseases within the study period had a prevalence of 26.7% (104/389). These included conditions classified as WHO clinical stage 2 to 4. Pulmonary Tuberculosis had a prevalence of 9% pneumonia had a prevalence of 3.6%, AIDS defining cancers 2.6% and HIVAN a prevalence of 2.3%.

Prevalence of HIV related disease by staging

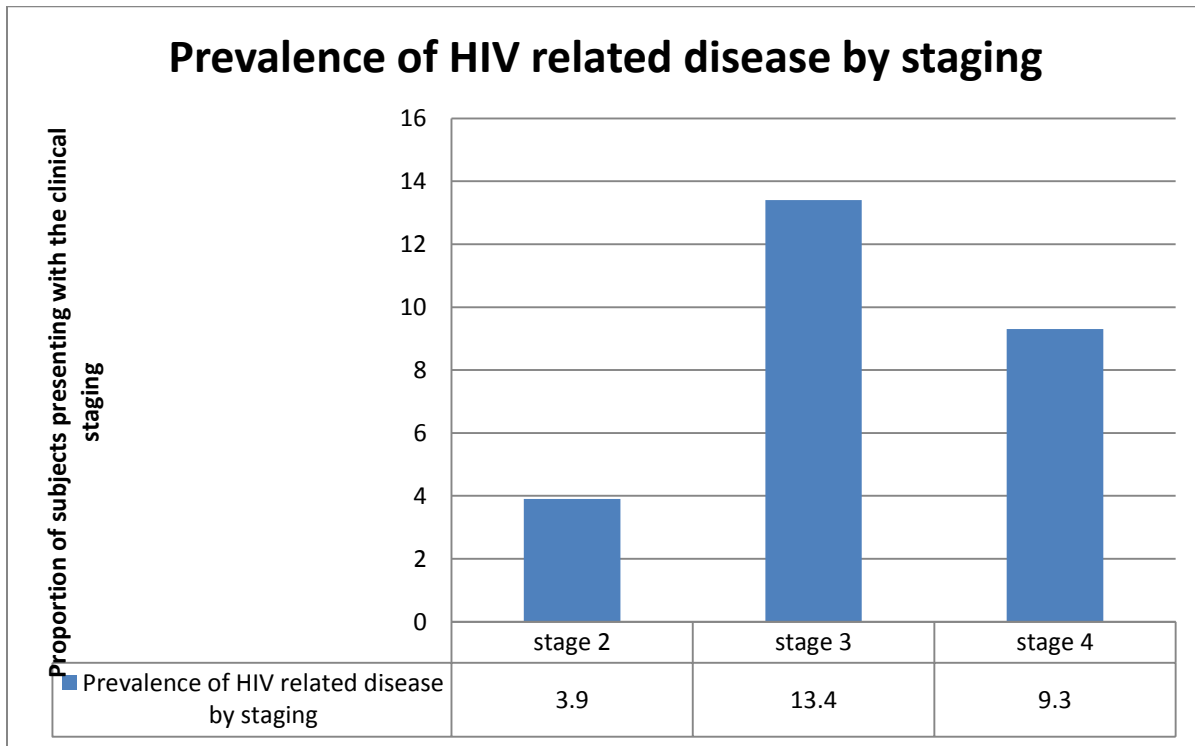


Figure 12- Prevalence of HIV related disease by staging

The prevalence of late stage opportunistic infections was 22.8% with those presenting with clinical stage 4 conditions being 9.4%. Of note, 30% of patients with HIV related disease of any stage were on HAART at the time

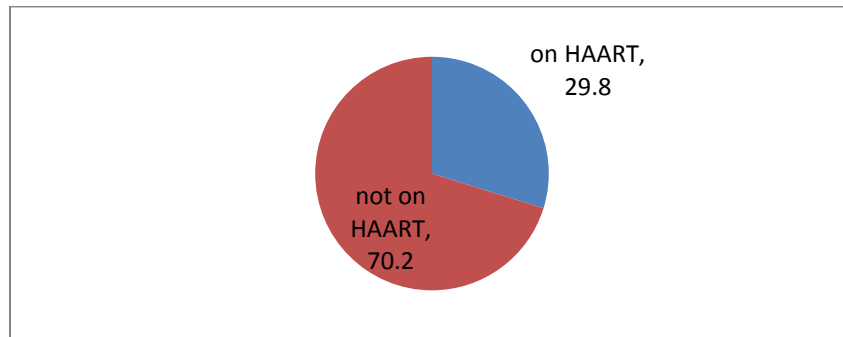


Figure 13- HAART status versus prevalence of HIV related disease

There was an association between the mean age and WHO clinical stage contrary to expectations, older age was associated with earlier stage at diagnosis. The median duration of treatment was similar for all three stages, with no demonstrated association.

	Current WHO stage			P value
	II	III	IV	
Mean age (SD)	60.8 (5.6)	56.0 (5.1)	57.0 (5.2)	0.008
Median duration of treatment (IQR)	16.0 (5.0- 40.0)	17.0 (9.0- 57.0)	19.0 (7.0- 47.0)	0.945

Table 10- Association between age, duration of treatment and clinical stage

4.8 Admission/ In-patient care

24.9% (97 /389) were admitted within the two year study period. Majority of subjects (73.2%) were admitted only once within the study period. 16% were admitted twice and 11% were admitted more than twice. Some patients were admitted with more than one condition.

Reason for admission

Prevalence of admission for infectious causes was 53.6% (52/97), non-infectious non-cancerous causes had a prevalence of 51.5% and admission for cancers ranked at 3.9%.

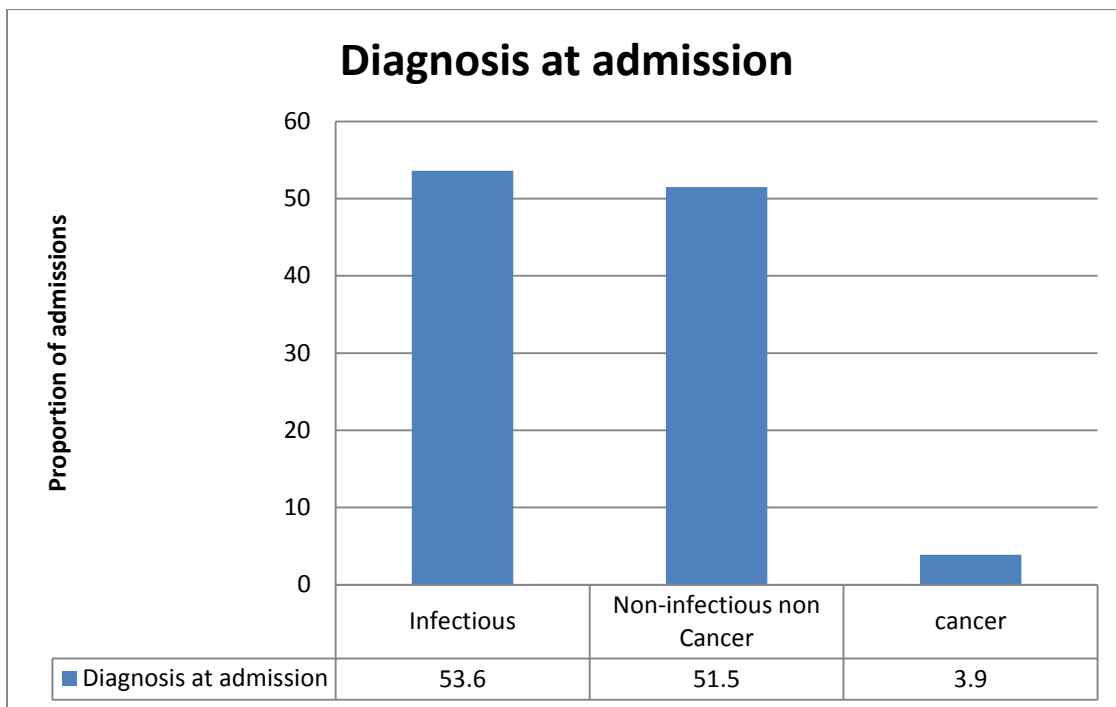


Figure 14- Diagnosis at admission

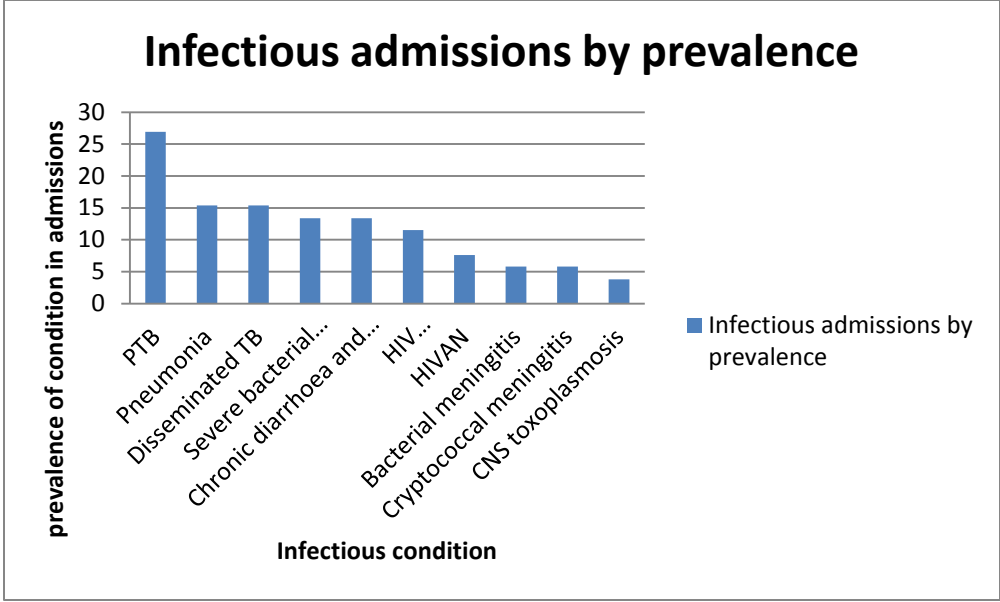


Figure 15- Infectious conditions leading to admissions

The commonest cause for admission was Tuberculosis, both pulmonary and disseminated. Infections that warranted in-patient care were all classified as WHO clinical stage 3 and 4.

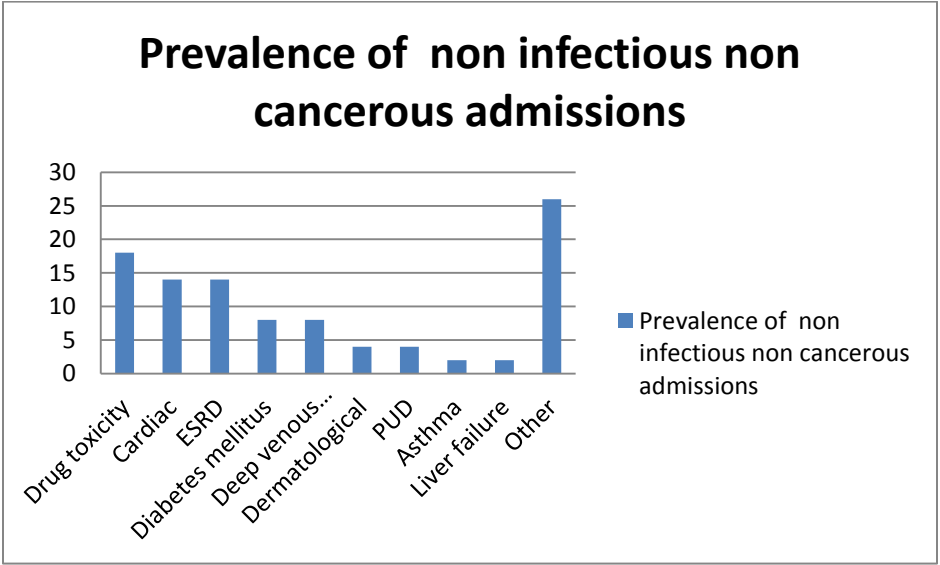


Figure 16- Prevalence of non-infectious non- cancerous admissions

Drug toxicity was the single leading cause of non-infectious non cancer admissions accounting for 18% of cases with a prevalence of 9% of all admissions. Cardiovascular disease and End stage renal disease (ESRD) also contributed significantly to inpatient morbidity. Those classified under ‘other’ causes of admissions were too diverse to be mentioned independently.

There were 15 admissions due to cancer, 10 were due to AIDs defining cancers and 5 due to non-AIDS defining cancers. Overall AIDs defining cancers were responsible for 66% of all cancer admission

Admitted with cancer	15(3.9)
Cervical cancer	3 (1.3)
Kaposi sarcoma	3 (0.8)
Non-Hodgkin’s lymphoma	2 (0.5)
Breast cancer	1 (0.3)
Tracheal cancer	1 (0.3)
Anal cancer	1 (0.3)
Hodgkin’s lymphoma	1 (0.3)
Mandibular cancer	1 (0.3)

Table 11- Cancer admissions

4.9 Outcome

2.6% had their last visit before the end of the study period and this was interpreted as loss to follow-up. 2.1% (8/389) died within the study period; 6 died from AIDS and 2 from non-AIDS causes. The median CD4 at enrollment for those who died within the study period was 43 cells/mm³ (7.8 -370.0) and median duration of illness was 12.5 months (10.0 -54.2).

Variable	Frequency (%)
Lost to follow-up	10 (2.6)
Mortality	8 (2.1)
Cause of mortality non-AIDS	2 (0.5)
Renal failure	1 (0.3)
Anal cancer	1 (0.3)
Mortality AIDS	6(1.5)
Chronic diarrhea and wasting	2(0.5)
Sepsis	1 (0.3)
Pulmonary TB	1 (0.3)
Disseminated TB	2 (0.5)

Table 12- Outcome

5.0 Discussion

This study set out to give an overview of the causes of morbidity and mortality in the HIV infected older adult at Kenyatta National Hospital; particularly the comparison of AIDS related and non-AIDS related morbidity and mortality.

The participants' age varied from 50-93 years as at 2011 with an average of 58.5 years. There was near equal representation of both men and women (0.96:1), in the randomly selected sample that blinded for sex, which contrasted with data on those aged less than 50 years that found the prevalence of HIV in women to be markedly higher than that in men (KDHS, 2008-2009).

Studies in Kenya and Malawi suggest an increased prevalence in men aged 50 -64 years (Negin *et al*, 2010, Freeman *et al*, 2012). This may account for the equal representation, but requires further research.

Majority of participants resided in Nairobi (65.8%) with 86.1% of participants having had some form of formal education. A significant number of the subjects subscribed to the Christian faith (89.7%) and 50% were married which is comparable to those aged 49 years and younger (KDHS, 2008-2009). In contrast, a third of participants were widowed, compared to 4.4% of women and 0.6% of men aged less than 49 years in 2008/2009 KDHS. A conclusive explanation was beyond the scope of this study.

The study demonstrated a steady increase in the proportion of newly registered older adults between 2011 and 2013 with an average of 8.7%; this is in keeping with the projection of an aging HIV epidemic (UNAIDS 2013). The proportion of persons who received services at the CCC within the study period was 16.5% (389/3908).

The median duration of illness at enrollment at the CCC was 52 months (21-88), with median CD4 counts of 186 cells/mm³ (85-316). Females were found to have a higher median CD4 count at enrollment of 207 cells/mm³ than males whose median CD4 was 145 cells/mm³; this is comparable with other studies that found higher CD4 counts in both HIV negative and positive women compared to men (Maskew *et al*, 2013, Maini *et al* 1996).

At enrollment, 85.1% were HAART naïve, 10.8% were on HAART and 3.9% were documented as defaulters. Those who were HAART exposed had higher CD4 counts at enrollment.

Nonetheless, despite the defaulters having a median CD4 count higher than that of HAART naïve subjects, a comparison between HAART status and WHO clinical staging at enrollment demonstrated that defaulters seemed more likely to present with late clinically (stage III and IV) with 86.5 % presenting in late stage; this is consistent with others studies (SMART study group, 2006). There was however, little difference between subjects presenting with late stage disease on HAART (40%) and those who were HAART naïve (46%) at enrolment. In this cohort, immune senescence leading to poor immune recovery must be considered in addition to traditional causes of treatment failure like genetic mutations and drug non- adherence (Grabar *et al*, 2002). Further research with more suited study designs are required to better assess this aspect.

As at the end of the study period, 93% of participants were on ART. 90 % of those on ART were on first line therapy. 40% of patients had been on more than one first line regimen. The number of first line regimens one had been on was associated with duration of treatment ($p = <0.001$).

10 % of those on ART were on second line therapy. This is significant as in this set up; third line therapy is not readily available. This study where demonstrated an association between being on second line therapy and duration of treatment where those who had been on treatment for a longer were more likely to be on second line therapy ($p=0.001$) In addition, defaulters were also more likely to be on second line therapy ($p=0.027$). This is consistent with other studies (Ajose *et al*, 2012). This is significant as the HIV epidemic continues to age; with longer survival on ART, it is expected that with time, a large proportion of PLHIV will be on second line therapy. It is estimated that 6% of PLHIV on first line therapy will require a switch to second line therapy every year in Sub-Saharan Africa (UNAIDS, 2013).

Chronic non-AIDS morbidity had a higher prevalence (74%) than HIV related disease (27%) overall. The prevalence of chronic non-AIDS morbidity was much higher than that found in a study carried out in Canada that encompassed adult PLHIV of all ages; it found a prevalence of 34% (Kendall *et al*, 2012). The prevalence of co-morbidity was 34% and that of multimorbidity was 39.6%, this was comparable to a study done in South Africa that found a prevalence of 34% of more than one comorbidity (Negin *et al*, 2012).

Despite the fact that only 27% of all participants had an AIDS related disease, it is worth noting that 50% of all diagnosed within the study period presented with late stage disease. These results were significantly different from a study done at Kenyatta National Hospital which found that 70.4% of all newly diagnosed adults presented in late stage disease, and only 29.6 % presented in the early stages (Ilovi *et al*, 2011). In addition, a study done in Italy found older adults to be more likely to be late testers (67%) than their younger counterparts (Longo *et al*, 2008). This discrepancy is likely due to the sampling frame which was obtained from the CCC rather missing

persons who may have been seen (admitted or died) at the hospital but not discharged through the center.

There was an association between duration of illness and the presence of multi-morbidity ($p=0.049$), but no association was demonstrated between increasing age and the same ($p=0.277$). This is possibly due to accelerated senescence caused by HIV with subsequent age related pathology due chronic inflammation (Deek 2011). There was no demonstrated association between gender and multimorbidity.

Cardiovascular disease had a prevalence of 36.8% among this population, of which hypertension was the leading contributor with a prevalence of 35.5%; this was comparable to results found in other studies, which found a prevalence of 30% in HIV infected adults in developing countries (Haregu *et al*, 2012). Metabolic disease ranked 3rd with a prevalence of 14.7% with Diabetes mellitus at 11.6% and Dyslipidemia at 5.7%; the prevalence of Diabetes in systematic reviews was lower 5% (Haregu *et al*, 2012). The risk factors for cardiovascular disease in HIV have been found to be a combination of traditional risk factors (i.e. life-style, sex and genetics), HIV disease itself and the toxic effects of ARVs (Muhammad *et al*, 2013). NNRTI and PI drugs contribute to cardiovascular and metabolic disease by altering lipid profiles (DAD study group, 2003). In addition, lipodystrophy, a common side effect of PI and NNRTI has been found to increase the risk of metabolic syndrome and insulin resistance (Hadigan *et al*, 2001). The prevalence of lipodystrophy in this study was 10.5%. The diagnosis of Metabolic Syndrome was not documented.

Documented renal disease other than HIVAN had a prevalence of 13.1% of which Chronic kidney disease (CKD) of unspecified staging had a prevalence of 10.8% and End stage renal

disease (ESRD) was at 2.3%. This compared to an overall prevalence of 11.5% of renal disease and 4.8% prevalence of ESRD among HIV positive patients in Western Kenya (Wools-Kaloustian K *et al*, 2007). Renal disease can be attributed to the natural process of aging, co-morbidities such as hypertension and diabetes as well as the HIV virus itself. Anti-retroviral drugs especially NRTIs are known to be nephrotoxic. In this study, drug nephrotoxicity had a prevalence of 5.1%. Tenofovir an NtRTI was the only documented cause of drug induced nephrotoxicity, with a prevalence of 6% of all who had ever used it. This is three times lower than the prevalence found in other studies (Fernandez- Fernandez *et al*, 2011). However, since Tenofovir has only recently been introduced as the first line therapy, replacing Stavudine, it is prudent to monitor its effects over time.

It is worth noting that Peptic ulcer disease and Osteoarthritis had high prevalence of 10.5% and 10.3% among subjects. Both are significant in terms of adding to the disease burden as well as possible drug interactions in their management as well as increase in pill burden.

Overall, the prevalence of polypharmacy was 70%, which was less than that found in a Swiss study of 82% (Marzolini *et al*, 2011). The prevalence of using one drug group was at 35%, two groups of drugs at 23% and three groups of drugs at 3%. There was no association demonstrated between age, sex, duration of treatment independently and polypharmacy. Despite the high prevalence of polypharmacy, there was only one documented case of drug interaction (0.3%). This may be due to prudent prescription of medication with minimum interaction or under-reporting.

The prevalence of adverse drug reactions was 21.6%. The commonest adverse effects were Lipodystrophy, nephrotoxicity and peripheral neuropathy occurring in 10.5%, 5% and 3.3% respectively. Stavudine was more likely to be associated with adverse effects; of all subjects had ever been on Stavudine (31.6%), an overwhelming 41.5% suffered from an adverse effect. The most predominant adverse effect was lipodystrophy. Since 2010, WHO recommended the phasing out of Stavudine due its disfiguring, long-term and life-threatening side effects (WHO, 2013). Tenofovir demonstrated a better safety profile; 70% of all subjects had ever been on Tenofovir and of these only 6.3% had an adverse effect. The only documented adverse effect occurring with Tenofovir was nephrotoxicity. Though given the high prevalence of chronic kidney disease in this age group, vigilance is required with the use of Tenofovir which is currently the first line therapy in Kenya (Ministry of Health, 2014)

A third of the subjects were diagnosed within the study period with 50% of those newly diagnosed within the study period presented with late stage disease at diagnosis. 26.7% of all subjects presented with HIV related disease. The leading cause of morbidity was pulmonary tuberculosis with a prevalence of 9% which was higher than the prevalence of TB in the general population of 7.1% (USAID, 2011). Pneumonia was also significant with a prevalence of 3.6%. HIVAN was reported in 2.3% of all respondents. Of note was that the prevalence of AIDS defining cancers was 2.6%, which was comparable to non-AIDS defining cancers which had a prevalence of 2.3% in this cohort. Considerably, 30% of the patients who presented with HIV related disease within the study period were on HAART; this is likely explained by treatment failure either due to traditional risk factors (gene mutations and non-adherence) or immune senescence (with poor immune recovery due to aging) (Grabar *et al*, 2002)

There was near equal prevalence in the cause of admission for AIDS and non-AIDS conditions which is an indication of the impact of HAART in reducing AIDS related morbidity. It compares to studies done that have found that HIV infected persons in the post-HAART era are suffering more and more from non-AIDS conditions than AIDS related morbidity (Collette *et al*, 2014) 25% of subjects were admitted within the study period. Majority, (73%) were admitted once, with 15.5% and 10.3% admitted two and three times respectively. The proportion of infectious causes was 53.6%, those due to non-infectious and non-cancerous conditions had an overall prevalence of 51.5% and cancer admission prevalence was 3.9%.

All the infectious conditions documented were WHO stage III and IV. In essence the prevalence of admission with late stage HIV was 53.6% of all admissions. Tuberculosis (both pulmonary and disseminated) remained a leading cause of morbidity in patient, HIV meningoencephalitis accounted for 11.5% of all infectious conditions.

Admission due to non-AIDS and non-Cancer related causes had a prevalence of 51.5% of all admissions. Of note, drug related toxicity was the leading single cause for admission (9.2% of all admissions) which was higher than Cardiovascular (7%), ESRD (7%) and Diabetes mellitus (4%). The likelihood of drug toxicity increases with age due to reduced body homeostasis with age as well as more pronounced drug effects (Turnheim *et al*, 2003).

2.6% of subjects were lost to follow up and 2.1% died. 8 persons died within the study period, 2 died from non AIDS related causes and 6 from AIDS related causes. The median CD4 at enrollment was 43 cells/mm³ and the average duration of illness was 15.2 months. Death was therefore associated with late diagnosis and generally shorter duration of illness from diagnosis to death. More appropriately designed studies are required to properly assess the causes of

mortality in older adults. Studies done in Kenya and Brazil have found that AIDS is still a leading cause of mortality among older adults in Nyanza province (Negin *et al*, 2012, Longo, 2008, Larceda, 2008). This contrasts with data from high income countries that suggest a marked decline of AIDS related deaths among PLHIV.

There were several strengths to this study; it was able to assess a large number of outcomes, it was relatively affordable and was carried out in a short period of time.

The study however, had a lot of limitations; being a retrospective study cross-sectional study, there are several confounding factors that were not accounted for. Subjects were not matched for age and sex with those HIV negative, to assess whether findings were truly significantly different due to their HIV status. In addition, data on younger HIV positive subjects was not collected to determine the significance of age. The study was also unable to draw causal inferences unless clearly documented e.g. adverse effects. Furthermore, missing data may have biased findings. The proposed sampling frame was a list of HIV positive persons seen at KNH provided by the Records' department. This list was unavailable and the sampling frame was therefore a list of persons seen at the CCC. This biased data as some patients may have been missed.

6.0 Conclusion

Over-all, the study demonstrated a double burden of disease in the HIV infected older adult, with a high prevalence of late stage disease at diagnosis (50%) and a high overall prevalence of chronic non-AIDS co-morbidities (74%). Polypharmacy had a significantly high prevalence which has an implication on pill burden, in terms of adherence and drug toxicity and should be addressed. Furthermore, AIDS related mortality was higher in this age group, though only 8 deaths were recorded in this period and this requires further study

7.0 Recommendations

Older persons require vigilance in drug prescription as drug toxicity was found to be a leading cause of non-infectious admissions. Furthermore, 50% of all newly diagnosed older persons were late testers and it is recommended that more efforts be geared towards education on HIV and testing among this population.

In closing, this study was not exhaustive and further studies should be carried out in terms of;

1. Clinical stage of disease at diagnosis for HIV infected older adults using a less biased sampling frame or a prospective design.
2. Wider studies should be carried out on poly-pharmacy, specifically the pill burden and drug interactions.
3. Drug toxicity in the HIV infected older adult
4. Prospective studies on immunological and virological progression of HIV infected older adults to determine the impact of immune senescence in our set up.
5. Similar studies should be carried out in rural settings for comparison

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Appendices

DATA COLLECTION SHEET

AN OVERVIEW OF THE CAUSES OF MORBIDITY AND MORTALITY AMONG HIV

INFECTED OLDER ADULTS AT KENYATTA NATIONAL HOSPITAL

Study number: _____

Date: _____

Social and Demographic Data

1. Date of Birth: _____

2. Sex: _____

3. Residence: _____

4. Level of education

- | | | | |
|-------------|--------------------------|-------------------------|--------------------------|
| (a) None | <input type="checkbox"/> | (c) Secondary | <input type="checkbox"/> |
| (b) Primary | <input type="checkbox"/> | (d) College/ university | <input type="checkbox"/> |

5. Religion

- | | | | |
|---------------|--------------------------|-----------|--------------------------|
| (a) Christian | <input type="checkbox"/> | (c) Hindu | <input type="checkbox"/> |
| (b) Muslim | <input type="checkbox"/> | (d) Other | <input type="checkbox"/> |

6. Marital status

- | | | | |
|-------------|--------------------------|-------------------------|--------------------------|
| (a) Single | <input type="checkbox"/> | (c) Separated/ Divorced | <input type="checkbox"/> |
| (b) Married | <input type="checkbox"/> | (d) Widowed | <input type="checkbox"/> |

7. Occupation

- | | | | |
|--------------|--------------------------|--------------------|--------------------------|
| (a) Employed | <input type="checkbox"/> | (c) Unemployed | <input type="checkbox"/> |
| (b) Retired | <input type="checkbox"/> | (d) Self- employed | <input type="checkbox"/> |

Treatment back-ground

8. CD4 at enrolment _____

(a) HAART naïve (b) HAART (c) Defaulter

9. WHO stage at enrolment: _____

10. WHO stage at diagnosis: _____

11. Duration since diagnosis: _____

12. Treatment:

12.1 ART: Yes No

If yes:

(a) First line Regimen _____

(b) Second line Regimen _____

(c) Total duration of treatment _____

12.2 Antibiotic prophylaxis

(a) Septrin

(b) Dapsone

(c) Isoniazide

12.3 Anti-fungal prophylaxis

Morbidity Data (06/2011 – 05/2013)

13. Chronic Non-AIDS defining Diseases

13.1 Cardiovascular Disease

(a) Hypertensive

(c) Heart failure

(b) Ischemic

(d) Other

13.2 Central Nervous System Disease

(a) Stroke

(c) Depression

(b) Dementia

(d) Other

13.3 Liver Disease

(a) Deranged Liver function tests

(c) Cirrhosis

(b) Liver failure

(d) Other

13.4 Renal Disease

(a) Chronic Kidney Disease other than HIVAN

(b) End stage Renal Disease

(c) Other

13.5 Urogenital

(a) BPH

(b) Uterine Fibroids

(c) Other

13.6 Skeletal

(a) Osteopenia (c) Bone fractures
(b) Osteoporosis (d) Other _____

13.7 Respiratory Disease

(a) Chronic Obstructive Airway disease (b) Other _____

13.8 Hematologic Disease

(a) Anemia (b) ITP (c) Other _____

13.9 Diabetes Mellitus

13.10 Dyslipidemia

13.11 Thyroid Disease

13.12 Other Chronic disease not listed _____

13.13 Non-AIDS defining Cancers (WHO criteria) _____

13.14 Total number of co-morbidities: _____

13.15 Polypharmacy Number of drugs _____

14. Adverse Drug Reaction

14.1 (a) Present (b) Absent

14.2 (a) Within study period (b) Prior to study period

14.3 Drug (s) in toxicity/ Drug interaction: _____

14.4 Nature of the adverse reaction: _____

15. HIV Disease

15.1 Opportunistic Infections (WHO criteria): Specify _____

15.2 AIDS defining cancers (WHO criteria): Specify _____

15.3 HIV virus: CNS _____

15.4 HIV peripheral Neuropathy _____

15.5 Renal (HIVAN) _____

16. Admissions

16.1 Admission Number of admissions _____

16.2 Reason for admission:

(a) Infectious _____

(b) Non-infectious non-cancerous _____

(c) Cancer _____

16.3 Loss to follow up _____

17. MORTALITY

17.1 Non-AIDS defining Disease (specify system) _____

17.2 AIDS _____

