CLINICOPATHOLOGIC FINDINGS OF CERVICAL CANCER AMONG HIV NEGATIVE AND POSITIVE PATIENTS SEEN AT MOI TEACHING AND REFERRAL HOSPITAL

BY

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A research thesis submitted in partial fulfillment of the requirements for an award of the degree of Master of Medicine in Reproductive health of Moi University, school of medicine.

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DECLARATION

I certify that this research thesis is my original work and has not been presented in any other university for the award of academic credit.

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DEDICATION

To my parents Mr. David Chebochok and Miss. Mary Kilonzo for their motivation and support during my academic Journey.

To my husband Mr. Joseph Mbithi and my three lovely children Brian Kimanthi, Michelle MutheuandBrayden Mwathe, for their love, encouragement and patience while undertaking this research.

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Abstract

Background: Cervical cancer is the third most common cancer in women worldwide with an estimated 530,000 new cases in 2008. In Kenya, it is the second most frequent cancer among women with an annual incidence of 2454 cases. It is the leading cause of cancer mortality in Kenyan women. At least 177 newly diagnosed cervical cancer patients were seen at Gyn-oncology clinic of MTRH in the year 2014. About 16.7 million women are living with HIV globally. In Kenya, the HIV/AIDs prevalence among women aged 15-64 years is 6.9%. The emergence of HIV/AIDS has altered the clinical features of cervical cancer and its effect on cervical cancer presentation is not well known in western Kenya.
Objective: To determine the difference in clinical stages and histological findings of cervical cancer between HIV positive and HIV negative patients seen at MTRH gyno-oncology clinic.
Methodology:This was a cross-sectional descriptive study conducted between February and August 2014 that involved clinical and histological examination of cervical cancer among 40 HIV positive and 40 HIV negative patients.Consecutive sampling was used to recruit histologically confirmed cervical cancer patients into each arm of the study. Structured interviewer administered questionnaires were administered to eligible participants to collect information on patient's biodata, clinical presentation and risk factor profile. Data on FIGO stage of cervical cancer, Histological type and degree of differentiation were obtained from the patient's file. Data was analyzed using SAS version 9.3.
Results: Cervical cancer presented 7 years earlier among the HIV positive patients 40(IQR: 34-46) years vs 47(IQR:40-55), P=0.0002. Overall, 52% of the patients presented with early cancer (FIGO stage I-IIA). About 25(63%) of HIV positive patients presented with early cancer as compared to 17(43%) of the HIV negative patients. Of the HIV positive patients, majority (48%) were in FIGO stage I; stages II, III and IVA comprised 12(30%), 8(20%) and 1(2.5%) respectively. Majority of the HIV negative patients, 16(40%) were in FIGO stage III; stages I, II and IVA comprised 11(27.5%), 12(30%), 1(2.5%) respectively. Squamous cell carcinoma was the predominant histological type 74(92.5%) for both groups, with 3 (3.8%) patients presenting with adenocarcinoma. Equal number of patients in both groups had well differentiated tumors 29%; of the HIV positive patients moderately differentiated tumors and poorly differentiated tumors accounted for 35% each while of the HIV negative patients 10(41.7%) and 7(29.2%) had moderately and poorly differentiated tumors.There was no statistically significant difference in the FIGO stage, histological type and the degree of differentiation of cervical cancer between the HIV positive and negative patient (p=0.073, p=1.000 and p=0.895 respectively). The commonest presenting symptoms were abnormal vaginal bleeding 53(66.3%) and abnormal vaginal discharge 16(20%) regardless of the HIV status.
Conclusion: HIV positive patients with cervical cancer were 7 years younger than the HIV negative patients. There was no significant difference in the FIGO stages, histological types and degree of differentiation of cervical cancer between the HIV negative and positive women.
Recommendations: A Cohort study should be conducted to establish the effect of HIV and HAART on the progression of cervical cancer in western Kenya.

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ABBREVIATIONS

ACCP-ALLIANCE FOR CERVICAL CANCER PREVENTIONCANCER PREVENTION.

AIDS- ACQUIRED IMMUNODEFICIENCY SYNDROME

AOR – ADJUSTED ODDS RATIO

ART- ANTIRETROVIRAL THERAPY

ASCUS-ATYPICAL SQUAMOUS CELLS OF UNDETERMINED SIGNIFICANCE.

ASIRS- AGE STANDARDIZED INCIDENCE RATES

CD4 – CLUSTER OF DIFFERENTIATION

CIN –CERVICAL INTRAEPITHELIAL NEOPLASIA

COC - COMBINED ORAL CONTRACEPTIVE PILLS

DNA- DEOXYRIBONUCLEIC ACID

E2 -EARLY GENE 2

E6 - EARLY GENE 6

E7 – EARLY GENE 7

FIGO- INTERNATIONAL FEDERATION OF GYNAECOLOGISTS AND OBSTETRICIANS

HAART- HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

HIV – HUMAN IMMUNO- DEFICIENCY VIRUS

HPV- HUMAN PAPILLOMA VIRUS

HR-HPV- HIGH RISK HUMAN PAPILLOMA VIRUS

HSIL- HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION

IARC- INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

ICC- INVASIVE CERVICAL CANCER

ICO - INSTITUT CATALÀ D'ONCOLOGIA

IREC- INSTITUTIONAL RESEARCH ETHICS COMMITTEE

KAIS- KENYA AIDS INDICATOR SURVEY

KDHS- KENYA DEMOGHRAPHIC HEALTH SURVEY

KNH – KENYATTA NATIONAL HOSPITAL

MOH -MINISTRY OF HEALTH

MTRH- MOI TEACHING AND REFFERAL HOSPITAL

NASCOP - NATIONAL AIDS & STI CONTROL PROGRAMME

OR- ODDS RATIO

PAPSMEAR- PAPANICOLAOU SMEAR

RB- RETINOBLASTOMA

SIL- SQUAMOUS INTRAEPITHELIAL LESION

UICC- INTERNATIONAL UNION AGAINST CANCER

UNAIDS-JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS

VIA- VISUAL INSPECTION WITH ACETIC ACID

VILLI - VISUAL INSPECTION WITH LUGOL'S IODINE

WHO- WORLD HEALTH ORGANIZATION

OPERATIONAL DEFINITION OF TERMS

Cervical Cancer- malignant neoplasm that arises from the cervix (the lower part of the uterus (womb) that opens at the top of the vagina.

Papanicolaou Test– a screening test used to detect pre-cancerous and cancerous processes in the cervix.

Clinico-pathologic - Combination of both symptoms reported by the patient and signs directly observable or found on physical examination by the physician and investigation findings.

HighRisk HPV/Oncogenic HPV–HPV types that are more strongly associated with cancer.

Multiparity– Having delivered two or more times.

Staging - The process used to find out if cancer has spread within the cervix or to other parts of the body.

Cervical Intraepithelial Neoplasia- A premalignant cervical disease that is also called cervical dysplasia or cervical Squamous intraepithelial lesions

Invasive Cervical Cancer- Cancer that has spread from the surface of the cervix to tissue deeper in the cervix or to other parts of the body.

Neoplastic Transformation-Conversion of a tissue with a normal growth pattern into a malignant tumor.

Immortalization-Thegaining of immunity to normal limitations on growth achieved by tumor cells.

Oncogenic– Thetendency to cause or give rise to tumors

Squamous Cell Carcinoma-A form of cancer that arises from the Squamous cells of the cervix.

Adenocarcinoma- A form of cancer that arises from the glandular cells of the cervix.

Squamo-Columnar Junction- Where the columnar secretory epithelium of the endocervical canal meets the stratified Squamous covering of the ectocervix. Most cervical cancers arise from this site.

Poorly Differentiated Tumor- Has cells that do not resemble the cell of origin- are primitive looking and unspecialized.

Well Differentiated-Tumor- Has cells resembling mature normal cells of the tissue of origin.

Adenosquamous-A type of cancer that contains two types of cells: Squamous cells and glandular cells.

Neuroendocrine-Areneoplasms that arise from cells of the endocrine (hormonal) and nervous systems.

CHAPTER ONE: INTRODUCTION

1.1 Background Information

Cervical cancer is the third most common cancer in women worldwidewith an estimated 530, 000 newcases in 2008(Arbynet al., 2011). More than 85% of cancer burden is in the developing countries with high cancer incidences in Africa of more than 50/100,000 populations. Eighty eight percent of the 275,000 global mortalities caused by cervical cancer in 2008 occurred in the developing countries with 53,000 occurring in Africa (Arbyn et al., 2011).There is a wide regional variation in age standardized incidence rates (ASIRs) of cervical cancer in Africa; 42.7/100,000 in Eastern Africa, 38.2/100,000 in southern Africa, 29.3/100,000 in Western Africa, 28/100,000 in central Africa and 12.1/100,000 in Northern Africa. (Arbynet al., 2011)

In East Africa theASIRs vary; Tanzania 50.9/100,000, Uganda 47.5/100,000, Rwanda 34.5/100,000, Kenya 23.4/100,000, Somalia 20.3/100000, Ethiopia 18.8/100,000 and Sudan 7/100,000. (Arbynet al.,2011).

In Kenya 2454 women are diagnosed with cervical cancer and 1676 die from the disease annually. This makes it the 2nd most frequent cancer among women in Kenya, and the leading cause of cancer mortality in women(Nairobi Cancer Registry, 2006).

Globally 16.7 million women are living with HIV (World Health Organization [WHO], 2011), these comprise more than 50% of all HIV infections. Sixty eight percent of all the HIV infections worldwide occur in Sub-Saharan Africa where Kenya lies(Joint United Nations Programme on HIV/AIDS[UNAIDS],2010).The prevalence of HIV in adults and

adolescents aged 15-64 years in Kenya is 5.6%. More women than men are infected in this age group; 6.9%vs. 4.4% respectively (Kenya Aids Indicator Survey [KAIS], 2012).The prevalence of HIV among cervical cancer patients was found to be 15% in KNH (Gichangi et al., 2003) which was more than twice the national prevalence of 6.7% at that time(Kenya National Bureau of Statistics [KNBS], Kenya 2003 Demographic and Health Survey[KDHS],2003).An unpublished study conducted in KNH among cervical cancer patients found a HIV prevalence of 47.3% (Fernandes, 2010).

In Kenya, the percentage of adults who need ART and are on it has been progressively increasing from 35% in 2007 to over 70% in 2012(KAIS, 2007; NASCOP, 2009; KAIS 2012). Use of Highly Active Anti-Retroviral Therapy(HAART) has not led to a decline in the incidence of cervical cancer, as compared to other conditions like Kaposi sarcoma and lymphoma (Clifford et al., 2005;Engels et al.,2006 ;Palefsky,Gillison & Strickler,2006) and has no effect on the progression of premalignant lesions to cervical cancer (De Vuyst, Lillo,Broutet&Smith,2008). However,HAART increases life expectancy and thus more HIV positive women live longer and are at risk of developing cervical cancer (Bor,Herbst, Newell &Bärnighausen, 2013).

Human papilloma virus(HPV) infection is the major risk factor associated with cervical cancer and is the most common sexually transmitted virus in the world responsible for 99.7% of cervical cancer cases (Walboomers et al.,1999;Sankaranarayanan,Thara,Esmy &Basu, 2008).Over 100 genotypes exist divided into Oncogenic/High risk (cause cancer) and non-Oncogenic(Bosch,Lorincz, Munoz,Meijer& Shah,2002).Generally the infection occurs in adolescence after the first act of sexual intercourse.HPV 16 and 18 account for 70% of cervical cancer cases (Munoz et al.,2004; Bosch et al., 2008). Most

immunocompetent women clear the infection. Those with persistent infection can progress todevelop premalignant lesions referred to asCervical Intraepithelial Neoplasia(CIN) which eventually progress to cancer of the cervix. Normally this process can take upto 10-15 years from onset of infection to development of cancer but with HIV this duration is shorter (van Bogaert, 2011).

In addition, HIV positive women are; five times more likely to have a high-risk HPV type (Moodley et al., 2006), infected with a broader range of HPV types (Clifford, Gary,Gonçalves, Maria & Franceschi, 2006) andmore likely to develop HPV-related cervical lesions and aggressive forms of cervical cancer (Danso, Lyons & Bradbeer, 2006).

This study seeks to establish current presentations of cervical cancer and compare these presentations between HIV positive and negative patients at Moi Teaching and Referral Hospital (MTRH).

1.2 Problem Statement.

Globally, cervical cancer is the 3rd most prevalent cancer among women, causing 530,000 cases and 275,000 deaths annually(Arbyn et al., 2011). In Kenya it is the leading cause of cancer mortality in women, causing 1676 deaths annually(Nairobi Cancer Registry, 2006). Cervical cancer epidemiology has been complicated by the emergence of HIV/AIDs with some studies reporting that HIV positive women are more likely to develop aggressive forms of cervical cancer and at an earlier age than the HIV negative women(Moodley et al., 2006; Clifford et al., 2006;Danso et al.,2006). Despite the above issues, there is limited data in the clinico-pathologic presentation of cervical cancer in context of HIV.

1.3 Research Questions.

1. Is there a difference in the clinical stages at presentation of cervical cancer between HIV positive and negative patients at MTRH?
2. Are the histological findings of cervical cancer different between the HIV positive and HIV negative patients at MTRH?

1.4 Justification.

The prevalence of HIV/AIDS in women aged 15-64 years is high in Kenya. On the other hand cancer of the cervix causes 2454 new cases annually. The emergence of HIV/AIDS has altered the clinical features of cervical cancer. There is paucity of data on the effect of HIV on cervical cancer presentation in Kenya.

Research on reproductive tract cancer is a priority research area according to the Kenya National Reproductive Health Research Agenda 2010-2014. MRTH was chosen because it has cervical cancer clinic serving an entire population of Western Kenya.This study will provide information on cervical cancer presentation in the context of HIV/AIDS.

1.5 Objectives

1.5.1 Main objective

To determine the difference in clinical stages and histological findings of cervical cancer between HIV positive and HIV negative patients seen at MTRH gyno-oncology clinic.

1.5.2 Specific Objectives

1. To compare the clinical stages at presentation of cervical cancer between HIV positive and negative patients at MTRH Gyno-oncology clinic.
2. To compare the histological findings of cervical cancer between the HIV positive andNegative patients.

CHAPTER TWO: LITERATURE REVIEW

2.1 Epidemiology of cervical cancer

Cervical cancer is the 3rd most common cancer in women globallywith an estimated 530 000 new cases and 275,000 deaths in 2008(Arbyn et al., 2011).The developing countries with only 5% of global resources account for over 85% of both cervical cancer cases and deaths (Lancet, 2010). It is the most common cancer inwomen in most developing countries and most common cause of cancer deaths (Cervical Cancer Action Report Card, 2011).

In sub-Saharan Africa it represents 22% of all cancers in women (Parkin,Ferlay and Hamdi-Cherif,2003). The incidence of cervical cancerin Africa is high with rates exceeding 50 per 100,000 populations and age-standardized mortality sometimes exceeding 40 per 100,000 populations.About 78, 897 women are diagnosed with cervical cancer annually, 78% of whom die from the disease.

There is a wide regional variation in age standardized incidence rates (ASIRs) of cervical cancer in Africa; 42.7/100,000 in Eastern Africa, 38.2/100,000 in southern Africa, 29.3/100,000 in Western Africa, 28/100,000 in central Africa and 12.1/100,000 in Northern Africa.

In East Africa the age standardized incidence rates vary; Tanzania 50.9/100,000, Uganda 47.5/100, 000, Rwanda 34.5/100,000, Kenya 23.4/100,000, Somalia 20.3/100000, Ethiopia 18.8/100,000 and Sudan 7/100,000(Arbyn et al., 2011).

In Kenya the population of women aged 15-64 years is 10.18 million(KNBS, Kenya - 2009 Kenya Population and Housing census) and are at risk of developing cervical cancer. Every

year 2454 women are diagnosed with cervical cancer and 1676 die from the disease making it the 2nd most frequent and the leading cause of cancer mortality in women. The annual number of new cases is projected to be 4261 in 2025 (Arbyn et al., 2011).

Globally 16.7 million women are living with HIV(WHO, 2011). In Kenya the prevalence of HIV has remained relatively stable since 2003. According to the K.A.I.S 2012, the prevalence in adults age 15-64 is 5.6%. Women are more likely to be infected with HIV than men with a prevalence of 6.9% vs 4.4% (KAIS, 2012). The number of HIV positive adults who need HAART and have been started on it has been progressively increasing from 35% in 2007to more than 70% in2012 (KAIS, 2007; NASCOP 2009; KAIS 2012). HAART has been proven to increase the adult life expectancy and thus more HIV positive women are living longer than was the case before the era of Anti-Retroviral Therapy(ART). HIV positive women have better immune response and lower risk of death than men following initiation of ART (Maskew et al., 2013). A study done in south Africa showed an increase in adult life expectancy from 49.2 years in 2003 before ART became available in the public-sector health system to 60.5 years in 2011-an 11.3-year gain. (Bor et al., 2013).

The prevalence of HIV among cervical cancer patients was found to be 15% in KNH (Gichangi et al., 2003), 32% in Uganda (Newton et al., 2001), 21% in Tanzania (Kahesaet al.,2008) and 21% among South African women(Moodley &Mould,2005). An unpublished study conducted in KNH among cervical cancer patients found a HIV prevalence of 47.3% (Fernandes,2010).

HAART has not led to a decline in the incidence of cervical cancer, as compared to other conditions like Kaposi sarcoma and lymphoma (Clifford et al., 2005;Palefsky et al.,2006;Engelset al.,2006). HPV is often stigmatized as a sexually transmitted infection (Khan et al., 2007).

HAART has little, if any, beneficial effect on the progression of cervical intraepithelial lesions (CIN) in HIV-positive women. Despite this fact, it increases their life expectancy and thus HIV positive women on HAART need to be monitored closely for HPV-related disease. (De Vuyst et al.,2008).

2.2 Risk factors of cervical cancer

HPV infection is the major risk factor associated with cervical cancer and the most common sexually transmitted virus in the world responsible for over 99% of cervical cancer cases (Walboomers et al., 1999; Sankaranarayanan et al., 2008). There are over 100 HPV subtypes (Bosch et al., 2002).The subtypes that cause cancer are referred to as Oncogenic/high risk while the non-Oncogenic ones don't cause cancer. The International Agency for Research on Cancer(IARC) of the World Health Organization has identified 13 genotypes i.e. 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 as having the highest Oncogenic potential (Bouvard et al., 2009).

HPV-16/18 are the most common accounting for >70% of ICC, followed by HPV types 31, 33, 35, 45, 52 and 58 which account for an additional 20% of cervical cancers worldwide (Munoz et al., 2004; Clifford et al.,2006; Bosch et al., 2008).

About 291 million women globally are carriers of HPV. In Africa, HPV infection prevalence is estimated at 21.3%, with significant variations from region to region: 33.6% in East Africa, 21.5% in West Africa and 21% in Southern Africa. In Kenya about 38.8%

of women in the general population are estimated to harbor cervical HPV infection at a given time, and 60.9% of invasive cervical cancers are attributed to HPVs 16 or 18. (WHO/ICO Information Centre on HPV and Cervical Cancer).

Both HIV 1 and 2 are associated with HPV infection (Langleyet al.,1996).HIV infection is associated with; High HPV viral load (Rousseauet al.,2007); an increased risk of persistent Oncogenic HPV infection and high incidence of High-risk HPV (Luchterset al., 2010).

HIV positive patients with low CD4 count have high incidence of HPV infections (Yamada et al., 2008)and invasive cervical cancer (Abraham et al., 2013). The mean CD4 counts for patients with cervical cancer are lower for HIV positive as compared to negative patients (Maimanet al., 1993;Gichangi et al., 2003).

Different studies give contradictory information on the HPV genotypes that cause cervical cancer in HIV positive women. Some studies have found similar HPV genotypes among the HIV positive women and negative women (Ng'andwe et al., 2007; De Vuyst et al., 2008) while others suggests that HPV genotypes, other than HPV 16 and 18, are frequently associated with cervical cancer in HIV positive women (Clifford et al., 2006; Sahasrabuddhe et al., 2007;Torneselloet al., 2008).

Some studies have shown ART to be associated with increased likelihood of regression of cervical dysplasia, decreased risk of progression of cervical cytologic abnormalities and enhanced clearance of HPV infections (Minkoff et al.,2001;Heard, Tassie, Kazatchkine &Orth,2002; Fife,Wu, Squires,Watts, Andersen & Brown, 2009; Paramsothy et al.,2009)

Others risk factors for cervical cancerinclude HIV, smoking, early age at first intercourse, multiple sexual partners, Multiparty, long term use of combined oral contraceptive (COC) and sexually transmitted infections.

In Kenya Median age at first sexual intercourse amongwomen (25-49 years) is 17.6 years (KNBS,KDHS 2008-09,2010).

According to a case control study done in Tanzania in 2007age at first coitus was not associated with cancer of the cervix. (Kahesa et al., 2007).

Abstinence from sexual activity and barrier protection during sexual intercourse have been demonstrated to decrease cervical cancer incidence (Berrington& Green, 2007) although condom use is only partially protective(Winer et al.,2006). Reduction in number of sexual partners and the use of condoms reduces risk for HPV infection (Burchell,Tellier,Hanley, Coutlee & Franco,2010; Nielson et al.,2010; Nyitray et al., 2011).

In women who are positive for cervical HPV DNA and who use COCs, risks of cervical carcinoma increase by up to fourfold compared with women who are HPV-positive and never users of COCs (Moreno et al., 2002), however this has been disputed in subsequent studies. A study by Syrjänen and his colleagues in 2006 concluded that the use of oral contraceptives was not an independent risk factor for cervical intraepithelial neoplasia or high-risk human papillomavirus infections(Syrjänen et al.,2006) and another study done by Kahesa and his colleagues in 2007 found no association between COC use and cervical cancer(Kahesa et al.,2008).

Women with seven prior full-term pregnancies have an approximately fourfold risk, and those with one or two have a twofold risk compared with nulliparas (Munoz et al., 2002). Gichangi and his colleagues in a case control study in KNH found that 68.9% ICC patients had five or more children as compared with 35% of controls(Gichangi et al.,2003). A study

done in Tanzania in 2007(Kahesa et al., 2008) found the mean parity of cervical cancer patients to be six and higher than in the controls.

Smoking was first hypothesized as risk factor for cervical cancer in 1977 by Winkelstein Jr.(Winkelstein Jr.,1977). Cervical cancer was listed among cancers causally related to smoking in 2004 by International Agency for Research on Cancer(International Agency for Research on Cancer [IARC], 2004).

Current tobacco smoking is associated with an increased risk of Squamous cell but not adenocarcinomaof the cervix. (International Collaboration of Epidemiological Studies of Cervical Cancer, 2006; Castellsagu´e et al., 2006;Gonz´alez, Sweetland &Green, 2004).

Among current smokers, the risk of being HPV-positive increases with increasing number of cigarettes smoked per day, and women who smoke 15 or more cigarettes daily have a 2-fold risk of HPV positivity as compared with never-smokers(Vaccarellaet al., 2008).

The number of cigarettes per day >10 cigarettes (as compared to smoking status and pack years of exposure) is most strongly associated with risk for CIN1 and CIN2-3. (Harris et al.,2004).

Xi and his colleagues in 2009 reported that higher HPV16 and HPV18 DNA load was associated with status of current, but not former, smoker (Xi,Koutsky& Castle,2009).

Cigarette smoking is an independent risk factor for infection with high risk HPV and not high grade cervical intraepithelial lesions (Syrjänen et al., 2007).

A study done in Tanzania in 2007 found that Women with cervical cancer were more likely to have ever smoked compared to the controls with an Odds Ratio (OR) of 5.3(Kahesa et al,2008).

2.3. Pathogenesis of cervical cancer

Cervical cancer results from abnormal and uncontrolled growth and replication of the cells in the cervix. Its onset is preceded by changes in the cervical cells called cervical intraepithelial neoplasia (CIN) which result from Human papilloma virus infection.This sexually transmitted virus infects the basal cells of the Squamous epithelium through tears or micro-tears in the skin or mucosa (Roberts et al., 2007). As basal cell layers migrate to the epithelial surface (either skin or mucosa), cells that contain infectious HPV virions have the potential for transmission to other persons or to other anatomical sites on the same person (McMurray, Nguyen, Westbrook, &McCance, 2001).

In most women the virus is generally eliminated by the immune system and thus most HPV infections resolve or become latent and undetectable (Moscicki et al.,1998; Evander et al., 1995;Ho, Bierman, Beardsley,Chang, &Burk, 1998). In contrast HIV positive women have immunosuppression and are at higher risk of persistent infections which predispose to cancer.

The integration of HPV genome into the host DNA leads to the expression of viral E2, E6, andE7 genes which lead to the production of proteins that initiate cell cycle and disable control ofgrowth, allowing the proliferation of genetic damage to accumulate in HPV infected cells. (Georgakilas, Mosley,Georgakila,Ziech&Panayiotidis, 2010).E6 and E7 have the ability to complex with the tumor suppressor genes p53 and Rb, respectively. The disabling of these two major tumor suppressor genes is thought to be central to host cell immortalization and transformation induced by HPV.

The risk of progression of premalignant lesions is higher in HIV positive patients especially if the CD4 count is < 200 cells/mm^3 (Duerr et al., 2006;Nappi et al., 2005).

Most early cancers are asymptomatic. Symptoms of advancing cervical cancer may include per vaginal bleeding, watery discharge, and signs associated with venous, lymphatic, neural, or ureteralcompression. Some patients may have history of post-coital bleeding.
HIV infection is associated with more extensive/larger volume of cervical involvement, and is also more likely to involve other areas in the lower genital tract (e.g. vulva, vagina, anal regions) (Maiman et al., 1990).

Studies that have been done previously in Kenya, report a median age 49.4 years (Were& Buziba,1999) and 47 years (Chirenje et al., 1998). More than 95% of the patients presented with tumor stage 2 and above. (Were & Buziba, 1999).

Women with HIV and cervical cancer tend to be 10—15 years younger than HIV-negative women with cervical cancer (Lomalisa,Smith& Guidozzi,2000;Moodley, M, Moodley, J.& Kleinschmidt,2001;Gichangi et al., 2003;van Bogaert, 2011).
Cervical cancer is recognized as an AIDS-defining illness (National Center for Infectious Diseases, 1992), and is a leading cause of mortality in HIVpositive women (PATH, 2007).

2.4. Clinical stages of cervical cancer

Cervical cancers are staged clinically. The staging system used in MTRH is the one developed by FIGO 2009. Its broadly divided into stages I, II, III and IV depending on the extent of cancer. Each of these stages is further sub-divided into; Stage I into IA1, IA2, IB1 and IB2; stage II into IIA1, IIA2 and IIB; Stage IIIA and IIIB and stage IVA and IVB(Pecorelli,Zigliani &Odicino,2009;Pecorelli, 2009). Early stage disease refers to

FIGO stages I through IIA which is surgically curable. The term advanced stage disease describes stages IIB and higher.

A case control study done in KNH found the distribution of the stages among the invasive cervical cancer (ICC) patients to be ;10% FIGO stage I, 43% stage II, 42% stage III and 6% stage IV. Among the HIV positive women with ICC 52% were FIGO stage II, 42% in stage III, while for HIVnegative women, about equal proportions, 41.2% and 41.6% were in stage II and III respectively.Twenty per cent (20%) of the HIVpositive patients were in stage I– IIA as compared to 23% of the HIVnegative patients. About 3.1% ofpatients in stage IIB and above had CD4 cell count < 200* 10^6cells/l as compared to 6% of the patients in stage I–IIA. (Gichangi et al.,2003).

According to a retrospective study done earlier in KNH of all the ICC patients , 6.4% were Stage I, 38.2% Stage II, 44.8% Stage III, and 10.6% Stage IV. Women in Stage 1 to Stage IIA were 3 years younger than those inStage IIB to Stage IV. (Gichangi et al.,2002).

HIV-positive women with invasive cervical cancer may present at more advanced stages (especially with CD4 <200/mm3), may metastasize to unusual locations (e.g.psoas muscle, clitoris, meningeal involvement), have poorer responses to standard therapy, and have higher

recurrences and death rates, as well as shorter intervals to recurrence or death, compared toHIV-negative women of similar stage (Maiman et al.,1990;Klevens, Fleming, Mays& Frey, 1996).

2.5. Histological types of cervical cancer

The diagnosis of cervical cancer is through biopsy. The two most common histological subtypes of cervical cancer are Squamous cell and adenocarcinoma regardless of HIV status.(Gichangi et al., 2003; Moodley et al, 2006). In a study by Gichangi and his colleagues, 48% of the histological subtypes were reported as poorly differentiated, 28% as moderately-well differentiated, 13% as well-differentiated and 11% as anaplastic. (Gichangi et al., 2002).

Different studies give conflicting results on the degree of differentiation of cervical cancer in HIV positive women. Some have associated HIV with poorly differentiated tumors (Gichangi et al., 2003; Matovelo,Magoma, Rambau, Massinde& Masalu, 2012). Other studies have found no difference with regards to HIV(Moodley et al.,2006).

2.6. Treatment

Invasive carcinoma of the cervix spreads primarily by direct extension and lymphatic dissemination. The therapy of patients with cervical cancer needs to address not only the primary tumor site, but also the adjacent tissues and lymph nodes. This is generally accomplished by either radical hysterectomy and pelvic lymphadenectomy, radiation with concomitant chemotherapy, or a combination thereof.

The mode of treatment depends on the FIGO stage regardless of the HIV status of the patient.

Patients with early stage cervical cancer (FIGO stage 1A2-11A) may be treated with both radical hysterectomy and pelvic lymphadenectomy or with primary radiation with concomitant chemotherapy.

Locally advanced cervical cancer (FIGO stage IIB-IVA) is treated with primary radiation (external beam plus brachytherapy) with concomitant chemotherapy. Patients with stage IVB and recurrent disease have a poor prognosis and are treated with a goal of palliation. Pelvic radiation is administered to control vaginal bleeding and pain. Systemic chemotherapy is offered to palliate symptoms.

2.7 Prevention

Cervical cancer is one of the most preventable and treatable cancers. The high number of cancer mortalities in the developing countries is because prevention programmes are either nonexistent or poorly executed (Alliance for Cervical Cancer Prevention [ACCP], 2004).Cervical cancer prevention strategies can be divided into; primary, secondary and tertiary as discussed below.

The primary prevention of cervical cancer is through vaccination. Two vaccines available were introduced in 2006; cervirax (bivalent, protects against HPV type 16 and 18) and Gardasil (quadrivalent) protects against 6, 11, 16, and 18). These vaccines are highly efficacious in preventing infection and clinical disease caused by two of the most pathogenic HPV genotypes, HPV16 and HPV18 (Garland et al., 2007; Giuliano et al., 2011; Villa et al., 2007; Palefsky et al., 2011).In December 2014, the United States Food and Drug Administration licensed the third HPV vaccine; Gardasil 9(HPV 9) which offers protection against HPV 6, 11,16,18,31,33,45,52 and 58. This covers more than 90% of cervical cancer causing HPV.

The WHO recommends adolescent girls of 9 to 13 years of age to be the primary target for vaccination and a 'catch-up vaccination' for a secondary target group of young women aged 14-26 (World Health Organization and United Nations Population Fund,2006). The upper age for HPV vaccination is debatable especially in places where HPV serology is not available (Schiffman,

Safaeian & Wentzensen, 2009). The Kenya National Cervical Cancer Strategic Plan 2011 -2015 recommends vaccination for ages 9-13 years. This is yet to be rolled out by the Division of Vaccine and immunization but piloting has been done. (Division of Reproductive Health[DRH]/ Ministry Of Public Health and Sanitation[MOPHS]/ Government of Kenya[GOK], Kenya National Cervical Cancer prevention program: Strategic Plan 2012 - 2015).

HIV-infected women are infected with less prevalent types of HR-HPV as compared to the general population(McKenzie, Kobetz,Hnatyszyn,Twiggs&Lucci,2010). There is also regional variation in HPV genotype distribution (Luque et al., 2010). This calls for a polyvalent vaccine for HIV positive women. (Sahasrabuddhe et al., 2007; Chaturvedi&Goedert, 2006).

The effectiveness of HPV vaccination in HIV positive women is likely to depend on the timing, with more benefits if it is given once HAART has been successfully initiated (Palefsky et al., 2006).

Secondary prevention of cervical cancer involves screening for and treatment of premalignant lesions and thus disrupting progression to cancer. The most recent KAIS reports screening coverage of 7.8% for women aged 15-64 years. HIV infected women are more likely to have been screened than the HIV negative women at 12.3% and 7.4% respectively (KAIS, 2012).

The Kenya National Cervical Cancer Prevention Program Strategic Plan 2012-2015 recommends screening targeting women aged 25-49 years with a frequency of 5years for HIV negative women. The screening cycle for HIV positive women to start at diagnosis, 6 monthly in the 1st year and then yearly if normal. The recommended screening approaches

for public health use in Kenya include Visual Inspection with Acetic acid(VIA)/ Visual Inspection with Lugol's Iodine(VILI), Pap (Papanicolaou) smear cytology and HPV testing (DRH/MOPHS/GOK- Kenya National Cervical Cancer prevention program: Strategic Plan 2012 -2015).

The optimal screening method for HIV positive women is unclear, but a study done in Western Kenya found VIAto be comparable to Pap smear and to be acceptable for screeningHIV-infected women in resource-limited settings(Mabeya et al.,2012).

Some studies suggest similar screening frequencies regardless of HIV status provided the HIV positive women have a normal initial cytology, are HPV negative and have CD4 counts >500cells/mm^3. This is because they have demonstrated that the cumulative incidence of pre-malignant lesions is the same for HIV negative and positive women who meet the three conditions (Harris et al., 2005,Keller et al., 2012).

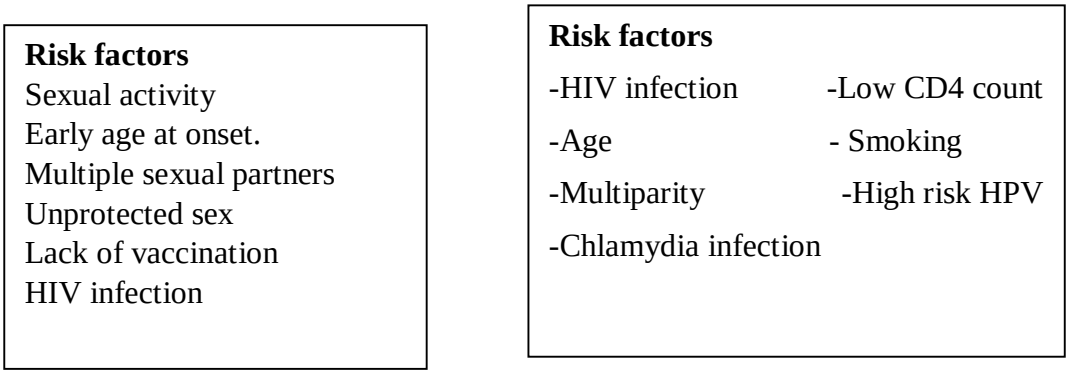
Anderson and his colleaguesin 2006 found that among women with normal results of Pap tests who underwent biopsy, the likelihood of cervical intraepithelial neoplasia was significantly greater for HIV-infected women (14.3%) than for HIV-uninfected women (1.2%).Ninety five percent (95%) of these women had abnormal Pap test findings (most often atypical squamous cells of undetermined significance) within 1 year of discordant cytologic and histological findings. These would have been detected using the current guideline on annual pap smears for HIV infected (Anderson et al., 2006).

Treatment of cervical intraepithelial neoplasia (CIN) in women with HIV (compared to HIV negative women) is associated with high failure and recurrence rates. This is

especially higher if the CD4 counts are less than or equal to 200cells /mm^3, the initial lesion was CIN 2, 3and those with detectable HPV after treatment (Massad et al., 2007).

Tertiary prevention of cervical cancer includes early diagnosis and treatment of cancer which depends on the stage at diagnosis as described under treatment above.

2.**8Conceptual framework**



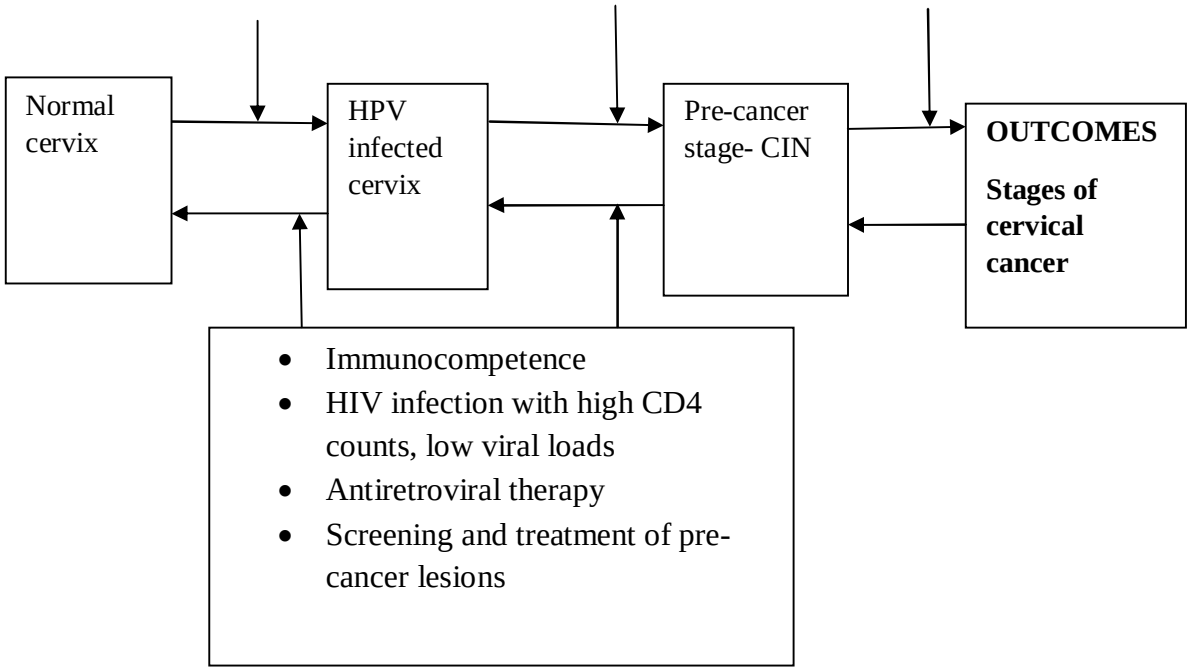


Figure 1. Modified cervical cancer progression model by Schiffman and Wentzensen, 2010 (Schiffman and Wentzensen, 2010).

The conceptual framework for this study is the modifiedcervical cancer progression model by Schiffman 2010. The risks factors affect the progression and development of cervical cancer at various stages. The main risk factor is presence of HPV and after the infection with HPV, most immune competent women clear the infection. In presence of risk factors, such infections may progress to pre-cancer and subsequently cervical cancer.

CHAPTER THREE: METHODOLOGY

3.1 Study design

This was a cross-sectional comparative study.

3.2 Study Setting

The study was conducted at the Moi Teaching and Referral Hospital(MTRH) gyno-oncology clinic. MTRH is the Second National referral hospital in Kenya located in Eldoret Town of Uasin Gishu County. It serves as a Teaching Hospital for Moi University's school of medicine,Kenya Medical Training College and Baraton University. It has a catchment population of 13 million people located in Western Kenya, parts of North-Rift and some parts of Eastern Uganda. It has several wards and outpatient clinics including the Gyno-oncology clinic which manages all patients with gyno-oncological malignancies including cervical cancer. The AMPHATH operates a network of cervical cancer screening clinics in Western Kenya, where all patients with suspicious cancer have biopsies taken and then referred to the gyno-oncology clinic. The gyno-oncology clinic runs on every Wednesday except on public holidays. Atleast 177 newly diagnosed cervical cancer patients were seen in the gyno-oncology clinic in 2014.

3.3 Study population

The study population comprised newhistologically diagnosed cervical cancer patients attending MTRH gyno-oncology clinic. During the study period 115 newly diagnosed cervical cancer patients were seen at the clinic of which 80 were recruited into the study.

3.4 Sample Size Determination

The sample size to compare the clinical stages of cervical cancer in the HIV positive patients to the clinical stages of the same condition in the HIV negative patients was computed using STATA version 12.The proportion of HIV negative subjects with locally advanced cervical cancer in stage IIB-IVA was found to be 74.5% (Cetina et al., 2006) according to international Federation of Gynecology and Obstetrics (FIGO) staging. It has

been reported that HIV positive women are five times more likely to have a high-risk HPV type than HIV negative women (Moodley et al., 2006). This means that the odds ratio of infection with HPV among the HIV positive women is 5. Thus we will use this knowledge to extrapolate the expected proportion of HIV negative patients with at least IIB of cervical cancer according to FIGO staging.

The expected number of subjects with advanced cervical cancer is 41% and 77.5% among the HIV negative and positive subjects, respectively. Using this information in the following sample size formula (Hulley, Cummings, Browner, Grady & Newman, 2007) we get 40 patients in each arm giving a total of 80 patients to be sampled.

$$n = \left[\frac{z_{1-\alpha/2}\sqrt{(p_1+p_2)(1-p_1+1-p_2)/2} + z_{1-\beta}\sqrt{p_1(1-p_2)+p_2(1-p_2)}}{p_1 - p_2} \right]^2$$

Where p_1 the proportion of HIV negative patients suffering from advanced cervical cancer and p_2 is the proportion of HIV positive patients suffering from advanced cervical cancer.

$z_{1-\alpha/2}$ is the $100(1-\alpha/2)$ percentile of the standard normal distribution under type I error while $z_{1-\beta}$ is the $100(1-\beta)$ percentile of the standard normal distribution under type II error.

$p_1 - p_2$ gives the effect size.

We need a total of n=80, in order to detect the true difference (effect size) between the two groups of subjects.The probability of wrongfully rejecting the null hypothesis when there

exist no difference between the proportions of HIV negative and HIV positive patients suffering from advanced cervical cancer was set to be 5%. The study was powered with 80% chance of being able to detect the existence of the true difference in the proportions of patients suffering from advanced cervical cancer between the two groups.

3.5 Eligibility criteria

3.5.1 Inclusion criteria

1. Confirmed HIV status
2. Aged 18 years and above

3.5.2.Exclusion criteria

1. Psychiatric patients who are unable to adequately provide medical history
2. Those who decline informed consent.

3.6 Study period

February to August 2014.

3.7 Sampling technique

Consecutive sampling was used to recruit newly diagnosed cervical cancer patients who met the inclusion criteria, into each arm of the study until the sample size of 40 in each arm was attained.

3.8 Data collection methods

Those who met the inclusion criteria were consented and interviewed in private consultation rooms by the researcher or research assistant.

Data was collected using interviewer administered structured questionnaires that were pretested in early February before beginning the study.

Structured questionnaire were administered to eligible participants to collect information on patient's biodata, clinical symptoms and risk factor profile. Data on FIGO stage of cervical cancer, Histological type and degree of differentiation were obtained from the patient's file. Patient's reported HIV status was counterchecked from the file.

3.9 Data Management

Data was maintained strictly confidential and restricted access only to the principal investigator and the research assistant. Questionnaires were kept in safe data cabinets with lock and key. The computer database was pass-worded to restrict access to unauthorized individuals. Filled Questionnaires will be destroyed by shredding after successful defense of the study findings or publication of study results, whichever comes first and computer databases and USBs will be deleted after 3 years.

3.10 Data analysis and presentation

Data analysis was done using SAS version 9.3. Categorical variables were summarized as frequencies and the corresponding percentages. Continuous variables that violated the Gaussian assumptions were summarized as median and inter-quartile range (IQR) while those which did not violate the Gaussian assumptions were summarized as mean and the corresponding standard deviation. Normality assumption was assessed using Shapiro-Wilks test for normality. Association between categorical variables were assessed using Pearson's Chi Square test while association between dichotomous variables and the continuous variables was assessed using Wilcoxon two sample test if the continuous variables violated the Gaussian assumption otherwise they were compared using the two-sample t-test. Associations with 2-sided $p<0.05$ were considered significant. Results were presented using tables and graphs.

3.11 Ethical considerations

1. The study was approved by IREC and management of MTRH/AMPHATH beforedata collection.
2. Informed consent was obtained from all participants in private consultation rooms.
3. Data management was maintained strictly confidential; locking questionnaires in lock and keys cabinets, pass wording the databases.
4. There were no conflicts of interest in this study.

CHAPTER FOUR: RESULTS

4.1 Sociodemographic characteristics

A total of 80 participants were included in the study. The median age was 42 (IQR: 36-51) years with a minimum of 27 and a maximum of 92 years. The distribution of the participants by the age groups was as shown in Figure 2.

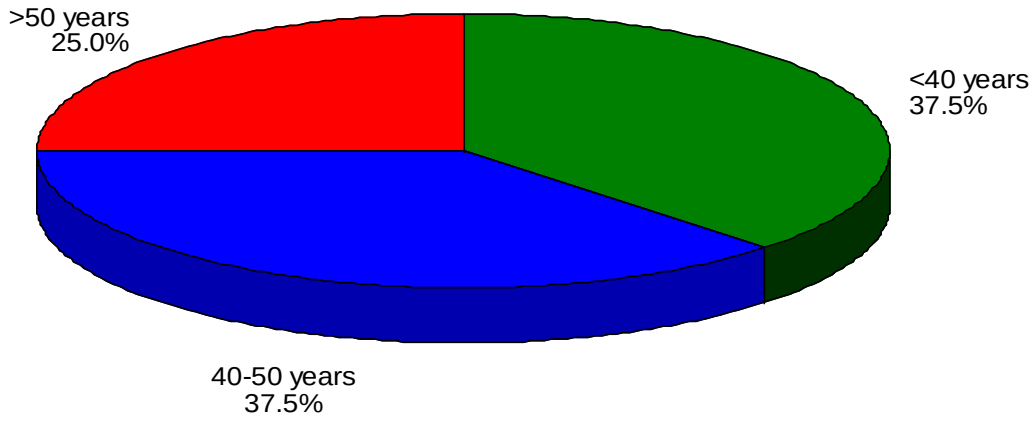


Figure 2: Distributionof participants by age groups.

HIV positive participants were seven years younger than the HIV negative participants, 40(IQR: 34-46)vs 47(IQR: 40-55) years, P=0.0002. The results further show that compared to the HIV negative, a higher proportion of HIV positive participants were aged <50 years, 36(90%) vs. 24(60%), P=0.005. The association between HIV status and demographic characteristics is shown in table 1 below.

In general, majority of the participants were married, 65(82%). The single and separated participants accounted for 6(8%) each. There were only 2(2.5%) widowed participants. The proportion of married participants among the HIV negative was significantly higher compared to the HIV positive, 37(92.5%) vs. 28(71.8%), P=0.016.

Table 1

Association between HIV status and demographic characteristics.

Variable	Sample size	Levels	HIV Positive n(%) or Median(IQR) or Mean±SD	HIV Negative n(%) or Median(IQR) or Mean±SD	P
Age	80		40(34-46)	47(40-55)	0.0002
Age (Grouped)	80	<40 years	20(50%)	10(25%)	0.005
		40-50 years	16(40%)	14(35%)	
		>50 years	4(10%)	16(40%)	
Marital status	79	Married	28(71.8%)	37(92.5%)	0.016
		Other	11(28.2%)	3(7.5%)	
Occupation	80	Housewife	14(35%)	15(37.5%)	0.093[f]
		Business	9(22.5%)	8(20%)	
		Farmer	5(12.5%)	10(25%)	
		Salaried employee	6(15%)	7(17.5%)	
		volunteers	6(15%)	0	
Education	79	None	2(5.1%)	5(12.5%)	0.692[f]
		Primary	15(38.5%)	15(37.5%)	
		Secondary	16(41.0%)	13(32.5%)	
		Post-secondary	6(15.4%)	7(17.5%)	
Religion	80	Catholic	10(25%)	6(15%)	0.264
		Protestant	30(75%)	34(85%)	

[f] "– Fisher's exact test P value was reported whenever the expected cell count was less than 5 in at least one cell in the created 2x2 table.

With regard to occupation, the highest proportion of study participants were housewives 29(36%), followed by businesswomen 17(21%), farmers 15(19%), salaried employees13 (16%).The "other" group representing 6(7.5%) was made up of one jobless, two volunteers, and three self-employed participants. Among the HIV negative, the housewives, farmers, and salaried employees were more compared to the HIV positive. All the self-employed and the volunteers were HIV positive. However, there was no statistically significant difference in occupation based on HIV status (P=0.093).

Less than one fifth of the participants, 13(16%) had post-secondary education. There were equivalent proportions of the participants who had primary and secondary levels of education accounting for 30(38%) and 29(37%) respectively. A small number did not have any formal education, 7(9%). Eighty percent representing 64 participants were Protestants while the rest were catholic. There was no association between HIV status and education (P=0.692) and HIV status and religion (P=0.264).

Majority of the respondent came from North rift valley, 33(44%) followed by Western, then Nyanza, and Southern and Central rift valley with the following representation, 18(24%), 15(20%), and 9(12%) respectively.

4.2 Risk factors of cervical cancer.

*Overall, t*here were 31(39%) participants who had ever been screened for cervical cancer. Table 2 below shows the association between HIV status and risk factors. Proportionately more HIV positive women had been screened as compared to the HIV negative, 17(42.5%) vs. 14(35%) but the difference was not statistically significant (p= 0.491). Whether a participant who underwent screening had a written report, whether the results were positive, and whether treatment was provided to those who had abnormal results were all not associated with HIV status, P=0.607, 0.488, and 0.100, respectively.

The average parity was 5±3 (mean±SD).The HIV negative participants had larger average parity 6± 3 compared to the HIV positive 4±2 children, P=0.003.

The median age at onset of sexual activity was 18(IQR: 17-20) years with a minimum of 12 and a maximum of 43 years, respectively. More than two thirds of the participants,

58(73%), had began sex before 20 years while one quarter 20(25%) started engaging in sex between the age of 30 to 40 years. The age at onset of sex was not different between the two groups p=0.988.

Table 2

Association between HIV statusand risk factors of cervical cancer.

Variable	**Sample size(n)**	**Levels**	**HIV Positive n(%) or Median(IQR) or Mean±SD**	**HIV Negative n(%) or Median(IQR) or Mean±SD**	**P**
Ever had cervical cancer screening	80	Yes	17(42.5%)	14(35%)	0.491
		No	23(57.5%)	26(65%)	
Have a written report	31	Yes	14(82.4%)	13(92.9%)	
		No	3(17.7%)	1(7.1%)	0.607[f]
Screening results	31	Normal	2(11.8%)	0	
		Abnormal	15(88.2%)	14(100%)	0.488[f]
Was treatment given to those with abnormal results	29	Yes	11(73.3%)	14(100%)	
		No	4(26.7%)	0	0.100[f]
Age at onset of sex	79		18(17-20)	18(17-20)	0.988
Age at onset of sex (grouped)	79	<20 years	28(71.8%)	30(75%)	
		20-30 years	11(28.1%)	9(22.5%)	0.703[f]
		>30 years	0	1(2.5%)	
Number of sexual partners	80		3(2-4)	2(1-3)	0.182
Number of sexual partners (grouped)	80	One	10(25%)	13(32.5%)	
		2-5	27(67.5%)	26(65%)	0.711[f]
		5-10	2(5%)	1(2.5%)	
		>10	1(2.5%)	0	
Parity	80		4(2)	6(3)	0.003

[f] "– Fisher's exact test P value was reported whenever the expected cell count was less than 5 in at least one cell in the created 2x2 table.

The median number of sexual partners was 2(IQR: 1-3) with a minimum of 1 and a maximum of 16 partners. There were 23(28.8%) participants who had one partner,

53(66.3%) participants with between 2-5 sex partners sex, 3(3.8%) with between 5-10 partners, and only one with >10 partners. Three quarters (75%) of the HIV positive patients had multiple sexual partners as compared to two thirds (67%) of the HIV negative women. However, the difference in the number of sexual partners was not statistically significant between the two groups, p= 0.182.

Only 3 (4%) participants had ever smoked; 2 HIV positive and 1 HIV negative. The difference however was not statistically significant, p=1.000.

4.3 Clinical symptoms of cervical cancer.

Table 3 shows the association between HIV status and clinical findings. Overall, two thirds of the participants 53(66.3%), had presented to the clinic because of abnormal vaginal bleeding while another one fifth of the participants 16(20%), had abnormal vaginal discharge. Five, 6.3%, of the participants had lower abdominal pain while 3(3.8%) complained of post coital bleeding. One participant complained of abdominal pains while another complained of uncontrolled urine. There was only one participant who had come for screening.

The median duration of symptoms was 90(IQR: 21-180) days overall. The HIV positive women presented slightly earlier than the HIV negative, 90(30-288) vs 105(14-180) days.

The difference in the clinical symptoms and the median duration of symptoms was not statistically significant between the HIV positive and negative women, P=0.276 and P=0.401 respectively.

Table 3
Association between HIV status and clinical findings.

Variable	Sample size(n)	Levels	HIV Positive n(%) or Median(IQR) or Mean±SD	HIV Negative n(%) or Median(IQR) or Mean±SD	p
Main Problem that brought the participant to the clinic	80	Abnormal vaginal bleeding	24(60%)	29(72.5%)	0.276[f]
		Abnormal vaginal discharge	8(20%)	8(20%)	
		Post coital bleeding	3(7.5%)	0	
		Others (Lower abdominal pain, Abdominal pains, Screening, Uncontrolled urine)	5(12.5%)	3(7.5%)	
Days the problem had lasted	76		90(30-288)	105(14-180)	0.401
Stages of the cancer	80	Stage I	19(47.5%)	11(27.5%)	0.141[f]
		Stage II	12(30%)	12(30%)	
		Stage III	8(20%)	16(40%)	
		Stage IV	1(2.5%)	1(2.5%)	
Stage of cancer (grouped)	80	Early cancer(I-IIA)	25(62.5%)	17(42.5%)	0.073
		Advanced stage(IIB-IVB)	15(37.5%)	23(57.5%)	
Histological type of cancer	80	Squamous cell carcinoma	37(92.5%)	37(92.5%)	1.000[f]
		Adenocarcinoma	1(2.5%)	2(5%)	
		Anaplastic	2(5%)	1(2.5%)	
Degree of differentiation	41	Grade 1	5(29.4%)	7(29.2%)	0.895
		Grade 2	6(35.3%)	10(41.7%)	
		Grade 3	6(35.3%)	7(29.2%)	

[f] "– Fisher's exact test P value was reported whenever the expected cell count was less than 5 in at least one cell in the created 2x2 table.

4.4 Clinical stages of cervical cancer.

About 53 % of the participants presented with early cancer (FIGO I-IIA), while 47% had advanced cancer (IIB-IVB). More HIV positive participants presented with early cancer as compared to the HIV negative, 25(62.5%) vs 17(42.5%) however the difference was not significant=0.073.This is shown in table 3 above.

Figure 3 below illustrates the clinical stages of cervical cancer for both the HIV positive and negative women. Majority of the participants were in stage I 30(37.5%), followed by stage II 24(30%)and stage III 24(30%). Only 2(2.5%) participants were in stage IVA. No participants were in stage IVB.Most of the HIV positive participants as compared to the HIV negative were in stage I 19(47.5%) vs 11(27.5%). Majority of the HIV negative were in stage III 16(40%) vs 8(20%) in the HIVpositive group. Equal number of participants in both groups were in stage II and IVA, 12(30%) and 1(2.5%) respectively. The difference in clinical stages of cervical cancer between the HIV negative and the HIV positive was not significant, P=0.141.

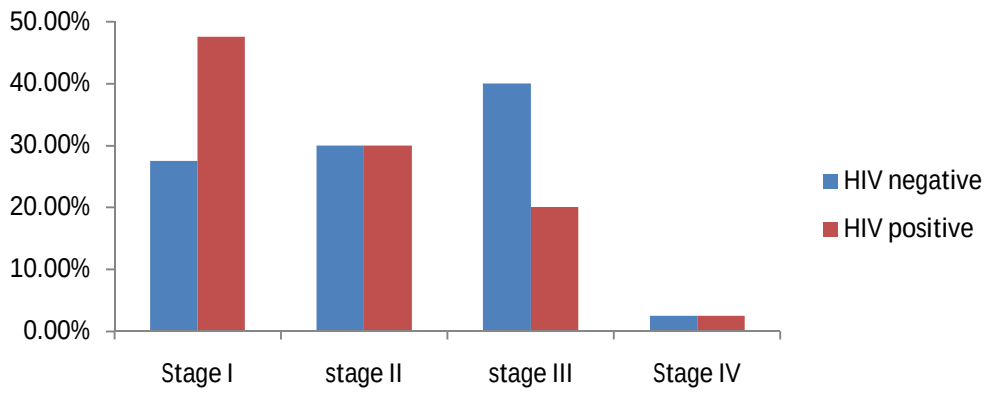


Figure 3.Clinical stages of cervical cancer for both HIV negative and positive participants.

4.5 Histological findings of cervical cancer.

The most predominant histological type of cancer was squamous carcinoma that was found in 74(92.5%) participants, followed by adenocarcinoma 4(5%) and anaplastic tumour 2(2.5%). Equal number of patients presented with squamous cell carcinoma as shown in figure 4. There was no difference in the histological types of cervical cancer between the HIV positive and the HIV negative, P=1.000.

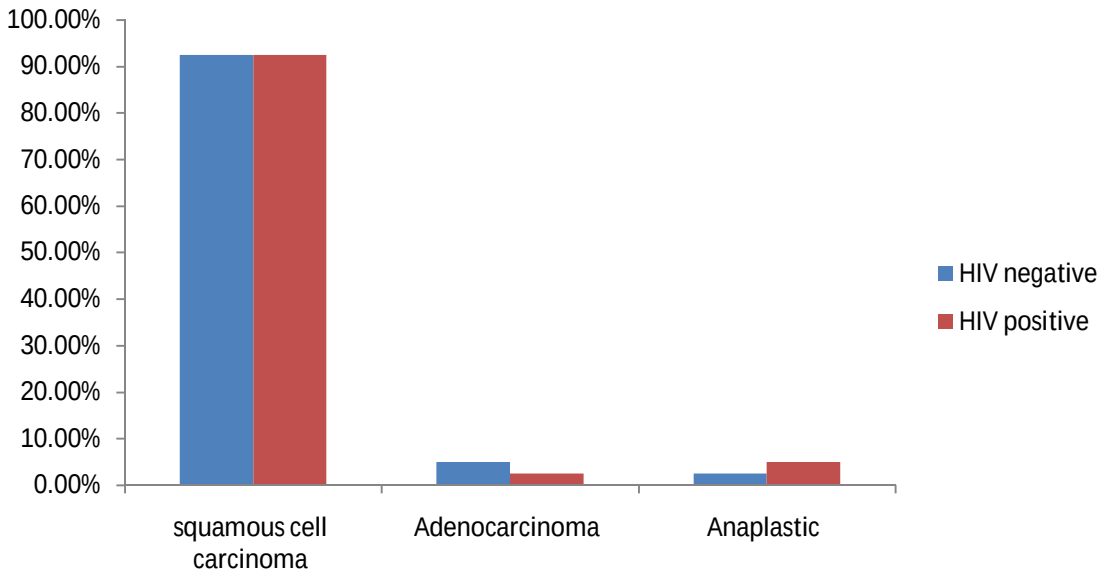


Figure4. Histological types of cervical cancer for both HIV negative and positive participants.

The degree of differentiation was recorded in 41(51%)of the participants. Majority of the participants 16(39%), had moderately well differentiated cancer (Grade 2) followed by poorly differentiated (Grade 3) cancer,13(31.7%) and well differentiated (Grade 1) cancer12(29.3%).

Majority of the HIV negative patients 10(41.7%),presented with moderately differentiated cervical cancer followed by poorly and well differentiated cancer in equal proportions 7(29.2%). For the HIV positive, most common was moderately and well differentiated cancer in equal proportions, 6(35.3%)followed by poorly differentiated cancer, 5(29.4%). This is illustrated in figure 5 below. However, the difference in the degree of differentiation of cervical cancer between the two groups, was not significant (P=0.895).

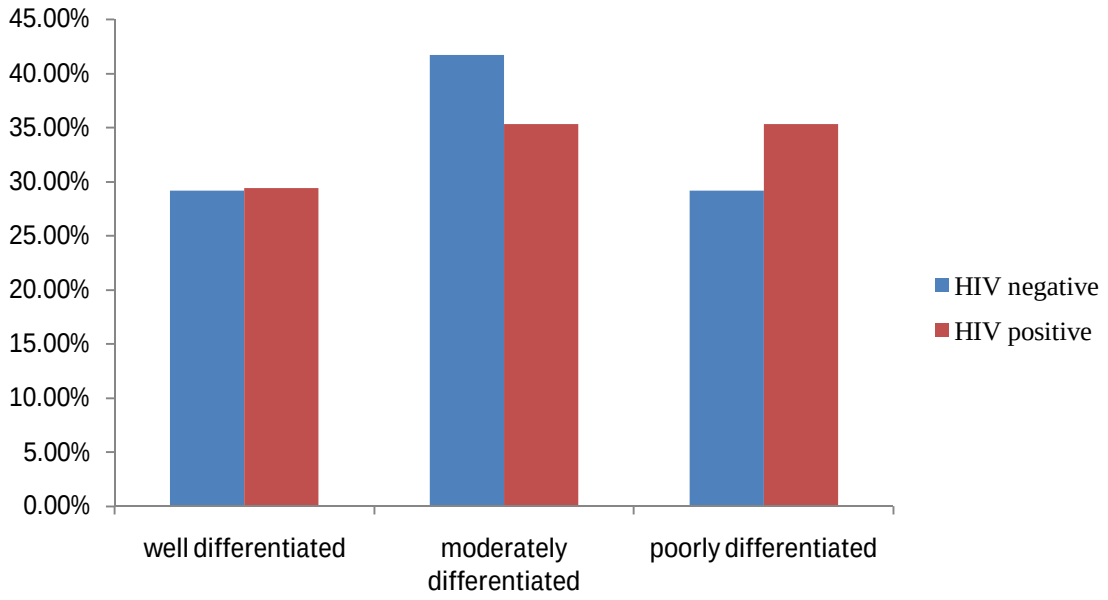


Figure 5.Degree of differentiation of cervical cancer for both HIV positive and negative participants.

4.6 Clinical characteristics of the HIV positive participants.

Only one participant had CD4 count of <200 cells/m^3. Majority of the participants 20(54.1%) had a CD4 count of >500cells/$mm^3$with the remainder 16(43.2%) havinga CD4of between 201-499 cells per cubic milliliter.

Of those who were HIV positive, 38(95%) were on HAART. They had been on HAART for a median duration of 36(IQR: 21-36) months with a minimum and a maximum of 3 and 96 months respectively.

Table 4 shows the distribution of clinical stages and histological findings by HAART and CD4 counts. The two patients who were not on HAART were all in FIGO stage I. Of the patients who were on HAART, majority 17(45%) were in FIGO stage I. The rest were in FIGO stage II 12(32%) and stage III 8(21%). Only one patient on HAART was in FIGO stage IV.

Table 4

Distribution of clinical stages and histological findings by CD4 levels and HAART use.

Clinical stages					
Variables	Levels	Stage I (n=19) n(%)	Stage II (n=12) n(%)	Stage III (n=8) n(%)	Stage IV (n=1) n(%)
CD4 (cells/m^3)	<200	0	0	1(14%)	0
	201-499	10(59%)	3(25%)	3(43%)	0
	>499	7(41%)	9(75%)	3(43%)	1(100%)
HAART	Yes	17(89%)	12(100%)	8(100%)	1(100%)
	No	2(11%)	0	0	0

Histological findings				
Variables	Levels	Squamous cell carcinoma (n=37) n(%)	Adenocarcinoma or papillary adenocarcinoma (n=2) n(%)	Adenocarcinoma or papillary adenocarcinoma (n=1) n(%)
CD4(cells/$m^{3)}$	<200	1(3%)	0	0
	201-499	14(40%)	2(100%)	0
	>499	20(57%)	0	0
HAART	Yes	36(97%)	1(100%)	1(50%)
	No	1(3%)	0	1(50%)

Degree of differentiation				
Variables	Levels	Grade 1 (n=5) n(%)	Grade 2 (n=6) n(%)	Grade 3 (n=6) n(%)
CD4(cells/$m^{3)}$	<200	1(20%)	0	0
	201-499	2(40%)	3(50%)	0
	>499	2(40%)	3(50%)	4(100%)

Majority of the HIV positive patients on HAART presented with squamous cell carcinoma 36(95%), one patient presented with adenocarcinoma and one with anaplastic tumor. Of those not on HAART one presented with squamous cell carcinoma and the other with anaplastic cancer. The number of HIV positive patients with degree of differentiation reported was too small for further analysis.

CHAPTER FIVE: DISCUSSION

5.1 Sociodemographic characteristics.

Previous studies have shown an association between HIV positive status and earlier more advanced cervical cancer. Case control studies by Kahesa and his colleagues in Tanzania and Gichangi and his colleagues in Kenyatta National Hospital found that HIV positive women were presenting with cancer of the cervix 10 years earlier than the HIV negative women (Kahesa et al., 2008,Gichangi et al., 2003).A retrospective study by Moodley in South Africa found that HIV positive women where presenting with cervical cancer 13 years earlier than the HIV negative(Moodley, 2006). The present study seems to be consistent with these studies as the HIV positive women presented with cervical cancer 7 years earlier than HIV negative women. The development of cervical cancer is preceded by cervical intraepithelial neoplasia(CIN) which results from HPV infection. The time taken from CIN to the development of cancer varies and may be upto 10-15 years. The plausible explanation for the early presentation of cervical cancer could be that the HIV positive women tend to have shorter pre-invasive period compared to HIV negative women. A prospective observational study conducted in South Africa found that the mean age at diagnosis of pre-malignant cervical lesions (LGSIL and HGSIL) was similar for both HIV positive and negative women. However, on follow up the study found that cervical cancer developed earlier in the HIV positive women (van Bogaert, 2011).In addition to the short pre-invasive period, HIV positive patients are five times more likely to have high-risk HPV types(Moodley et al., 2006), more likely to develop HPV related cervical lesions and more aggressive forms of cervical cancer(Danso et al.,2006). Also, HIV positive women have reduced immunity and thus may not be able to clear HPV infections as their HIV negative

counterparts. Furthermore, immunosuppression even from other causes increases cancer risk (Kessler, Jan, Molle&Guillemin, 2006). It predisposes HIV positive women to persistent oncogenic HPV infection and high incidence of High-risk HPV as compared to HIV negative women(Luchters et al., 2010).Persistent HPV infections predispose one to developing cancer of the cervix.

In general majority of the cancer patients had primary and secondary education. Majority were unemployed.However,there was no significant difference in the occupation, education and religion among the cervical cancer women in respect to their HIV status. A finding that is consistent with previous studies (Gichangi et al., 2003).

Significantly more HIV negative women with cervical cancer were married as compared to the HIV positive women. This finding differed from previous studies, by Gichangi ,Kahesa and their colleagueswho found no difference in marital status between HIV positive and negative women(Gichangi et al., 2003; Kahesa et al., 2008). The plausible explanation for this could be that generally HIV prevalence and risk of infection is higher among un-married women as reported by Shisana et al in sero-prevalence survey conducted in South Africa(Shisana,O.,Hall,E.J., Maluleke,R., Chauveau,J., &Schwabe,2004). Also the recent KAIS 2012 found HIV prevalence to be high among separated or divorced women as compared to married or cohabiting women 12.5% vs 4.8%(KAIS, 2014).

5.2 Risk factorsof cervical cancer

Cancer of the cervix is caused by HPV infection which is sexually transmitted, however not all women with HPV infection develop cervical cancer. Several factors have been

found to modify the progression from HPV infection to cancer development. These include parity of 5 and above, smoking and use of oral contraceptives for more than five years (Bosch& de Sanjosé, 2007). Previous studies have found women with cervical cancer to be of parity of 6 and above(kahesa et al., 2007;Gichangi et al.,2003). This study found the mean parity of the cervical cancer patients to be 5 overall which is consistent with previous studies. However, how increasing parity predisposes to cervical cancer is not clear. Possible explanations could be that hormonal changes during pregnancy cause immunosuppression that could increase risk of HPV infection and progression to pre-cancer and cancer lesions. Furthermore, parity has been suggested to be a marker of the estrogen hormonal environment during the fertile years of women and estradiol has been reported to induce immortalization of HPV infected cells and hence predispose to cancer development (Newfield, Bradlow,Sepkovic&Auborn, 1998). In addition to that, recurrent cervical trauma with subsequent healing as occurs in women of high parity could make cells vulnerable to carcinogenic effect of HPV.

Very few studies have reported on parity in relation to HIV in cervical cancer patients. The current study found that HIV negative women were significantly of a higher parity than HIV positive women. A finding that was similar to a study by Gichangi and his colleagues in 2003 who found that 73% of HIV negative women to have a parity of more than 4 as compared to 43% of HIV positive patients,$p<0.001$(Gichangi et al., 2003). The plausible explanation could be that HIV and parity being both risk factors of cervical cancer could play a synergistic role or that HIV positive women develop cervical cancer before they can attain their desired family sizes.

Regular cervical cancer screening has been shown to reduce incidence of cervical cancer and cancer mortalities.Atashili and his colleagues in 2011 used a transition model to quantify the potential effect of screening on cervical cancer mortality and found that screening even when done once, had the potential to reduce ICC mortality(Atashili et al.,2011).This study found that only 39% of the cervical cancer patients had been screened with a higher proportion of those who had had screening being the HIV positive 43% vs 35%. However the difference was not statistically significant. This proportion was higher than that reported in a case control study at KNH (Gichangi et al., 2003), which found that only 20% of ICC patients had been screened with significantly more being HIV positive than HIV negative,31% vs 19%, p=0.047.The KAIS 2012 found that a higher proportion of HIV positive women had been screened compared to HIV negative at 12.3% and 7.4 % respectively (KAIS, 2014). The higher numbers in this study could be because of the Cervical Cancer Screening Program (CCSP) that covers western Kenya where most of the study subjects come from or a general increase in cervical cancer screening.

Previous studies have shown an association between HPV infection and the number of partners more than three (Martins et al., 2014). HPV is the main risk factor for cervical cancer and is sexually transmitted. This study did not find a significant difference in the number of sexual partners between HIV positive and negative women, a finding that was consistent with previous studies (Gichangi et al., 2003).

Early age at onset of sexual activity increases the risk of developing Cervical cancer later in life with some studies reporting 3-4 fold increased risk if sexual debut is at <18 years as compared to 20 years and above(Green et al., 2003; Sierra-Torres,Tyring & Au, 2003). This study found the median age at onset of sexual activity to 18 years for both HIV

positive and negative women with cancer of the cervix. This is similar to what has been reported in demographic surveys in Kenya. Studies comparing age at onset of sexual activity between HIV positive and negative womenwith cervical cancer are scarce.Kahesa and his colleagues in 2008 did not find an association between cervical cancer and the age at onset of sexual activity (Kahesa et al., 2008).

Cervical cancer was listed among cancers causally related to smoking in 2004 by IARC (IARC, 2004). Subsequent studies have linked cigarette smoking to a higher risk of Oncogenic HPV infection, premalignant cervical lesions and squmous cell carcinoma (Castellsagu´e et al., 2006; Harris et al., 2004;Syrjänen et al., 2007). Smoking was not a major risk factor in our setting because only 4 % of patients reported history of smoking(2 HIV positive and 1 HIV negative) which was not significantly different between HIV positive and negative women. This is similar to what Kahesa and his colleaguesfound in a study in Tanzania (Kahesa et al.,2008). Gichangi and his collegues found 6% of cervical cancer women were smokers but smoking was not associated with cervical cancer, he did not compare smoking and HIV status (Gichangi et al., 2003).

5.3Clinical symptoms of cervical cancer.

Overall abnormal vaginal bleeding was the commonest presenting symptom (66%) of cervical cancer, followed by abnormal vaginal discharge (20%). Other symptoms include abdominal pains, urine incontinence. Very few patients had been diagnosed with cancer through screening. This study found no significant difference in the presenting symptoms between the HIV positive and negative women. Similar findings though higher proportions were reported in a cross-sectional study done in Uganda that found vaginal bleeding and

abnormal vaginal discharge as the commonest presenting symptoms, 82.5% and 70% respectively(Mugisha, 2012). This study was only conducted among HIV positive women.

Overall, median duration of symptoms before initial visit was 90 days (3 months) with half of the patients seeking care by six months. Mugisha's study in Uganda found a higher proportion (90%) of patients presenting within six months and nearly half of the patients presenting within the first month (Mugisha, 2012). Our study found no significant difference between HIV positive and negative women, but HIV positive women presented slightly earlier, 90 vs 105 days. This could be because HIV positive women have regular clinic visits.

5.4 Clinical stages of cervical cancer.

Cervical cancer patients are staged clinically using the FIGO 2009 staging system (Pecorelli etal., 2009; Pecorelli, 2009). There are four major stages (I, II, III&IV) which are further subdivided each into A and B. The stage at presentation of cervical cancer determines the mode of treatment and prognosis with early cancer (FIGO stage I-IIA) having a better prognosis than advanced cancer (IIB-IVB).

Previous studies on stage at presentation in relation to HIV status give conflicting results with some reporting that HIV positive women present with more advanced disease than HIV negative women while others report that HIV positive women report with early disease while others have found the stages at presentation comparable. A retrospective study in a HIV clinic in Kisumu- Kenya found that more than 90% of HIV positive women diagnosed with cervical cancer during screening had stage IA1 disease however this study did not have a comparison group (Mungo, Cohen, Maloba, Bukusi, & Huchko, 2013).

In the current study, more HIV positive patients presented with early cancer as compared to the HIV negative 63% vs 43%. These proportions were higher than the findings of Gichangi and his colleagues who found slightly more HIV negative than positive patients presenting with early cancer 23% vs 20%(Gichangi et al., 2003). In this study, most of the HIV positive women (48% vs 28%) presented with stage I cancer while most of the HIV negative patients (40% vs 20%) presented with stage III cancer. This was different from what Gichangi and his colleaguesfound in KNH where 52% of the HIV positive patients presented with stage II while most HIV negative patients presented in stage II and III ,42% each(Gichangi et al.,20003). However in both studies the difference in clinical stages at presentation was not statistically significant.

The finding that more HIV positive patients are presenting earlier is possibly due to the fact that HIV positive women are on regular clinic visits and thus have an opportunity to report their symptoms early and access diagnostic workup early. It's also possible that HIV positive women have been educated on cervical cancer symptoms and the importance of early presentation and are also screened more. In areas with comprehensive screening programs the prevalence of cervical premalignant and malignant disease is comparable between the women living with HIV and HIV negative patients(Thorsteinsson et al., 2014). This means that if all women were to have regular screening then probably there will be no difference in stages of cervical cancer at presentation.

5.5. Histological findings of cervical cancer.

Overall the commonest histological type of cervical cancer is the squamous cell followed by adenocarcinoma (Gichangi et al., 2003; Moodley, 2006). This study found that most patients presented with squamous cell cancer regardless of HIV status.

The degree of differentiation of cervical cancer cells is a prognostic factor. Overall, majority of the patients presented with moderately differentiated cancer. Previous studies have reported that HIV positive women have poorly differentiated cancer compared to the HIV negative (Gichangi et al., 2003;Matovelo et al., 2012). This study found no significant difference in the degree of differentiation of cervical cancer among HIV positive and negative clients which is consistent with a retrospective study in South Africa (Moodley, 2006). The assessment of degree of differentiation could have been limited by numbers since only about 50% of the patients had degree of differentiation reported.

5.6 Clinical characteristics of the HIV positive participants.

Majority of the HIV positive clients were using HAART, for a median duration of 36months.This proportions are higher than the findings of cross-sectional studies done in KNH in 2010,which found only 52% of the HIV positive patients with invasive cervical cancer were on HAART(Fernandes, 2010) and in Uganda which found 75% of the patients on HAART(Mugisha, 2012). Use of HAART has not been shown to change the progression of premalignant cervical lesions to invasive cervical cancer (De vuyst et al., 2008). Further, the use of HAART has not reduced the incidence of cervical cancer among the HIV positive women as has been the case with other HIV related cancers such as Kaposi Sarcoma and Non-Hodgkin'sLymphoma (Clifford et al., 2005, Shiels et al., 2011).

Despite HAART having no impact on the natural history of cervical cancer, it prolongs lifespan for HIV infected women which makes them at a higher risk of developing cancer. A study done in Uganda did not show an association between HAART duration and clinical stages of cervical cancer(Mugisha, 2012). The number of HIV positive patients not on HAART in this study where small for analysis of association of HAART and clinical findings.

HIV positive women with CD4 counts of <200cells/mm^3 have more than seven times increased incidence of invasive cervical cancer as compared to uninfected women(Abraham et al., 2012). In addition, thesewomen have increased risk of Squamous intraepithelial lesions- the precursor of cervical cancer (Swende, Ngwan, & Swende, 2012). A study in KNH found that a higher percentage of HIV positive patients (17%) had CD4 cell count < 200cells/mm^3 as compared with 0.9% of HIV negative patients and a mean CD4 of more than 500cells/mm^3 which was comparable to that of sero-positive patients without cervical cancer(Gichangi et al., 2003). Another study in KNH in 2010 found the mean CD4 count of HIV positive cervical cancer patients to be 304cells/m^3 (Fernandes, 2010).

This differed with the current study where nearly all HIV positive clients with cervical cancer had a CD4 count of more than 200 with more than half having a CD4 count of 500 cells/m3 and that only one patient had a CD4 count of <200 cell/m3. The high CD4 counts in this study could be explained by the fact that nearly all (95%) our sero-positive patients were on HAART for a median duration of 36 months.

Gichangi and his colleaguesfound a positive association between CD4<200cells/m^3 and poorly differentiated cervical cancer(Gichangi et al., 2003). A descriptive study done in Tanzania found that HIV positive patients with early cancer had significantly more CD4 counts(385 vs 266 cells/m^3) than those with advanced cancer and that patients with poorly differentiated tumors were six times more likely to be HIV infected(Matovelo et al., 2012).In this study the small numbers did not allow analysis of the association between the CD4 level and the clinical and histological findings of cervical cancer among the HIV positive women.

5.7Study limitations

Only about half of the patients had the degree of differentiation of cervical cancer reported. This could have interfered with the findings of this study in that aspect.

The study relied on patients reporting on symptoms, duration, age at first sexual intercourse. This can be affected by recall bias.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Cervical cancer presented 7 years earlier in the HIV positive patients. HIV positive patients were more likely to develop cervical cancer at an age less than 40 years.

There was no significant difference in the FIGO stages, histological types and degree of differentiation of cervical cancer between the HIV negativeandpositive women.

The commonest presenting symptoms were vaginal bleeding and vaginal discharge, regardless of the HIV status.

HIV negative women had a higher parity than the HIV positive and were more likely to be married.

Majority of the women had not been screened for cervical cancer and this was not different between HIV positive and negative.

6.2 Recommendations

There is need to improve completeness of histological data of cervical cancer.

A Cohort study should be conducted to establish the effect of HIV and HAART on the progression of cervical cancer in western Kenya.

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APPENDICES

APPENDIX 1: IREC APPROVAL

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
SCHOOL OF MEDICINE
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference: IREC/2013/61
Approval Number: 0001016

27th June, 2013

Dr. Doris Nthenya Mbithi,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
APPROVED
27 JUN 2013
P.O. Box 4606 ELDORET

Dear Dr. Mbithi,

RE: FORMAL APPROVAL

The Institutional Research and Ethics Committee have reviewed your research proposal titled:-

"Clinicopathologic Findings of Cervical Cancer among HIV Negative and Positive Patients seen at Moi Teaching and Referral Hospital."

Your proposal has been granted a Formal Approval Number: **FAN: IREC 1016** on 27th June, 2013. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; it will thus expire on 26th June, 2014. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

01/07/2013

DR. W. ARUASA
VICE-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc:	Director	-	MTRH
	Principal	-	CHS
	Dean	-	SOM
	Dean	-	SPH
	Dean	-	SON
	Dean	-	SOD

APPENDIX 2: IREC AMENDMENT

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
SCHOOL OF MEDICINE
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference: IREC/2013/61
Approval Number: 0001016
15th April, 2015

Dr. Doris Nthenya Mbithi,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
15 APR 2015
APPROVED
P.O. Box 4606-30100 ELDORET

Dear Dr.Doris,

RE: APPROVAL OF AMENDMENT

The Institutional Research and Ethics Committee has reviewed the amendment made to your proposal titled:-
"Clinicopathologic Findings of Cervical Cancer among HIV Negative and Positive Patients at Moi Teaching and Referral Hospital".
We note that you are seeking to make an amendment as follows:-

- Rewording research questions, broad and specific objectives.
- Addition of study hypothesis

The amendment has been approved on 15th April, 2015 according to SOP's of IREC. You are therefore permitted to continue with your research.

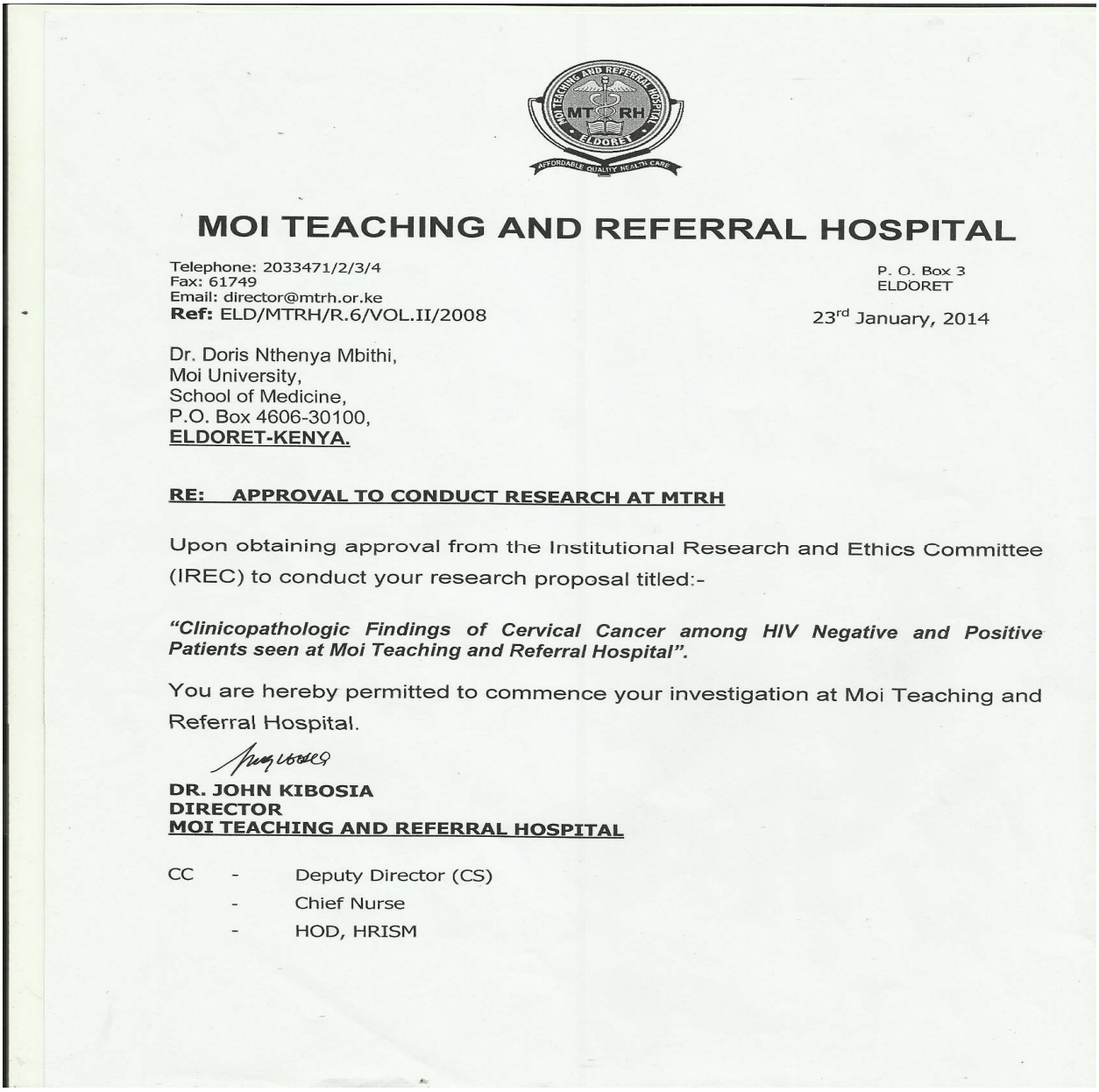
You are required to submit progress(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change(s) or amendment(s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

16/04/2015
Dr. WILSON ARUASA
DEPUTY CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc: Director - MTRH Dean - SPH Dean - SOM
Principal - CHS Dean - SOD Dean - SON

APPENDIX 3: APPROVAL TO CONDUCT RESEARCH AT MTRH



MOI TEACHING AND REFERRAL HOSPITAL

Telephone: 2033471/2/3/4
Fax: 61749
Email: director@mtrh.or.ke
Ref: ELD/MTRH/R.6/VOL.II/2008

P. O. Box 3
ELDORET

23rd January, 2014

Dr. Doris Nthenya Mbithi,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

RE: APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:-

"Clinicopathologic Findings of Cervical Cancer among HIV Negative and Positive Patients seen at Moi Teaching and Referral Hospital".

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

DR. JOHN KIBOSIA
DIRECTOR
MOI TEACHING AND REFERRAL HOSPITAL

CC - Deputy Director (CS)
- Chief Nurse
- HOD, HRISM

APPENDIX 4: CONSENT FORM

My name is Doris Nthenya Mbithi and currently I am pursuing my Masters Degree at Moi University. A requirement of this course is to do a dissertation. I chose to study clinical findings of cervical cancer among HIV positive and Negative patients. I will ask you questions about your socio demographic and reproductive health characteristics. I will also ask you about your illness. You are free to respond or choose not to respond to some of the questions that you may find inconvenient to you.

Are you willing to participate in the study?…….. Signature……

Kiambatisho 11: **CHETI CHA KUTOA IDHINI KWA HIARI**

Jina langu ni Doris Nthenya Mbithi na sasa niko kutafuta Shahada ya Uzamili katika Chuo Kikuu cha Moi. Moja ya mahitaji ya masomo haya nikufanya tasnifu, nami nimeamua kuchunguza matokeo na dalili za kiafya ya saratani ya mlango wa uzazi miongoni mwa kina mama wanaoishi na virusi vya ukimwi na wasiokuwanao. Ninaenda kukuuliza maswali juu ya kijamii na afya yako ya uzazi. Pia nitakuuliza kuhusu ugonjwa wako.Una uhuru kujibu au kutojibu baadhi ya maswali ambayo unaweza kupata hayakupendezi.

Unakubali kujumuishwa katika uchunguzi huu?.....Sahihi……..

CONFIDENTIALITY OF INFORMATION

Your participation in this study will not affect in any way the treatment plan that your doctors have planned for you.Your decision to participate will not change or prejudice your

care in the hospital.This study is a minimal risk study and it has more benefits than harm. The risks involved in this study are social and psychological risks. There is no legal risk in this study since it is a voluntary participation with adequate informed consent.Information gathered will be treated with utmost confidentiality; your identity will be protected (your name will not be used and you will be identified with a number, only known to me and my immediate assistant). The information obtained will be used to improve services in the clinic and may be published in medical journals and/or presented in scientific symposia (both local and international).

The Moi University Ethics and Research Committee has approved this study

For any question or clarification, please do not hesitate to contact me on 0720439089 or contact the chairperson of IREC, MOI TEACHING AND REFERAL HOSPITAL BUILDING, second floor room 219 P.O BOX 3-30100 ELDORET. Phone number 0787723677.

USIRIWA HABARI

Ushiriki wako katika utafiti kwa njia yoyote hautaadhiri mpango wa matibabu ambao madaktari wameamua unakufaa. Kukubali kwako kushiriki au kutokubali hakutaadhiri matibabu yako katika hosipitali hii.Utafiti huu una hatari kidogo sana na manufaa yake ni mengi kuliko madhara. Madhara ambayo yanahusishwa na utafiti huu ni ya kijamii na kisaikologia. Hakutakuwepo na madhara ya kisheria kwa sababu kushiriki katika utafiti huu ni kwa hiari baada ya kupata maelezo kamili kuhusu utafiti huu. Taarifa zitakazopatikana zitawekwa fiche, na hazitatambulishwa kwa vyovyote (jina lako halitatumika bali ni herufi itakayotumika ambayo itajulikana kwangu mimi na

msaidiziwangu wa karibu pekee). Taarifa itakayopatikana itatumika kuboresha huduma kwenye kliniki, na pia yaweza kuchapishwa kwenye majarida ya matibabu au kuwasilishwa katika makongamano ya kisayansi (ya humu nchini na kimataifa).

Utafiti huu umeidhinishwa na Kikao cha Maadili naUtafiti cha Chuo Kikuu cha Moi (IREC).Kwaufafanuzi au swali lolote, tafadhali usisite kuwasiliana nami kwenye nambari hii:0720439089;au kuwasiliana naMwenyekiti wa IREC,JENGO LA MOI TEACHING AND REFERAL HOSPITAL,OROFA YA PILI -CHUMBA 219, S.L.P 3-30100, ELDORET. NAMBARI YA SIMU- 0787723677.

APPENDIX 5: DATA COLLECTION FORM

QuestionnaireNo:……Date of interview……

SECTION A: SOCIO-DEMOGRAPHIC CHARECTERISTICS

1. How old are you ?.....
2. What is your marital status (a)Single (b)Married (c) Separated (d) Widowed
3. Which county do you reside? ……..
4. Whats your occupation? (a) housewife (b) business (c)farmer (d)salaried employee (e) other (please specify)……
5. What is your highest level of education ? (a)none (b)primary (c) secondary (d)Post secondary
6. What is your religious affiliation? (a)catholic (b)protestant (c) Muslim(d) other

SECTION B: SYMPTOMS

7. What was main problem that brought you to the hospital? (a) Abnormal vaginal bleeding (b) Abnormal vaginal discharge (c) Postcoital bleeding (d) Other (please specify)……
   …
8. For how long have you been having the above problem? (a) …….days (b)……..weeks (c)……months (d) …….years (e) I don't know

SECTION C: RISK FACTORS

9. How many times have you got pregnant (Parity)…….
10. Do you know your HIV status?.....
11. HIV Status……..
12. If HIV positive I)CD4 counts a)<200 (b)201-499 (c)> 500
    II)viral load……
13. Are you on HAART? (a) yes (b) no
14. If yes to quiz 13, For how long?.....
15. Have you ever smoked? (a) Yes (b) No (c) Don't remember
16. Are you currently smoking?(a) Yes (b) No (c) No comment

17.If currently smoking, how many cigarettes per day?.....

18.Have you had any cervical cancer screening test (a)Yes (b) No (c)don't know

19.If yes, specify which one (a) VIA (b) Papsmear

20.What were the results of the screening test you had? (a) Normal (b) Abnormal (c) Don't know?

21.Do you have any written report of the results?

22.If the results were abnormal, were you given any treatment?

23.What was your age at onset of sexual activity? ……

24.On average, How many sexual partners have you had?……

25.Have you ever had a sexually transmitted infection ? (a) Yes (b) No (c) Don't remember.

APPENDIX 5: HOJAJI

No.ya Hojaji:…….Tarehe……

SECTION A: JAMII

1. Umri wako ni miaka mingapi?…….
2. Hadhi yako ya ndoa ni ipi? (A) Sijaolewa (b) Nimeolewa (c) Nimetengana na mme wangu (d) Mjane
3. Unaishi kaunti gani? ……..
4. Njia yako ya kujipatia riziki ni ipi? (a) Mke wa nyumbani (b) biashara (c)mkulima (d)kazi ya kulipwa kwa mwezi (e) nyingine (fafanua)……
5. Umefikia kiwango gani ya elimu? (A) Sina elimu yoyote (b) elimu ya msingi (c) elimu ya upili (d) elimu ya kupisha sekondari
6. Dini lako ni lipi? (a)Ukatoliki (b)Kiprotestanti (c) Muislamu (d) Nyingine (fafanua)……

SEHEMU YA B: DALILI ZA UGONJWA

7. Shida kubwa iliyo kuleta hospitalini ni ipi? (a) kuvuja damu kwenye uke (b) Uchafu kwenye uke (c) kuvuja damu kwenye uke kila baada ya ngono (d) Nyingine (fafanua)……
8. Dalili hizo ulizipata kwa muda gani? (a) siku……. (b)wiki…….. (c)miezi……(d)miaka ……(e) Sijui

SEHEMU YA C: MAMBO YANAYOCHANGIA

9. Umekuwa mja mzito mara ngapi? …….
10. Je, wajua hali yako ya virusi vya Ukimwi?.....
11. Hali hiyo ni ipi? ……..
12. Ikiwa unazo virusi vya Ukimwi, (I) Idadi ya (a) CD4 <200 (b) CD4 201-499 (c) CD4> 500 (II) kipimo cha virusi_____
13. Je, unatumia madawa ya kupunguza makali ya Ukimwi(HAART)? (a) Ndio (b) La
14. Ikiwa jibu lako ni Ndio kwa swali 12, ni kwa muda gani? …….....

15. Umewahi kuvuta sigara? (a) Ndio (b) La (c) Sikumbuki

16. Je, kwa sasa unavuta sigara?(a) Ndio (b) La (c) Sisemi

17. Ikiwa unavuta sigara kwa sasa,unavuta vijiti ngapi kwa siku moja?.....

18. Je, umewahi kupimwa saratani ya mlango wa uzazi? (a) Ndio (b) La (c)Sijui

19. Ikiwa umewahi kupimwa,fafanua nikipimo kipi(a) VIA (b) Pap smear

20. Matokeo ya kipimo hiki yalikuwaje? (a) Yalikuwasawa (b) Hayakuwasawa (c) Sijui

21. Je, unaripoti yoyote iliyoandikwa ya matokeo hayo?.....

22. Ikiwa matokeo hayakuwa sawa, ulipewa matibabu yoyote?.....

23. Ulikuwa na umri gani ulipoanza kushiriki ngono? ……

24. Kwa wastani, umekuwa na wapenzi wangapi unaoshiriki ngono nao?……

25. Je, umewahi kupata ugonjwa wazinaa?(a) Ndio (b) La (c) Sikumbuki

SECTION D: FIGO STAGE OF CERVICAL CANCER(from medical records)

26. Stage of cervical cancer
(a) Stage I A…….IB…….

(b) stage II A…….IIB…….

(c) stage III A……..IIIB……

(d)stage IV A…….IVB…….

SECTION E: HISTOLOGY

27. Histological type of cervical cancer(From medical records)

(a)Squamous cell carcinoma

(b) Adenocarcinoma

(c)Adenosquamous

(d) Others histolological types (specify)……

SECTION F: DEGREE OF DIFFERENTIATION(tumor grade)

28.The degree of differentiation of cervical cancer cells

(a)Well differentiated (grade 1)

(b)Moderately well differentiated (grade 2)

(c) Poorly differentiated(grade 3)