CLINICOPATHOLOGICAL CHARACTERISTICS OF HIV POSITIVE AND HIV NEGATIVE PATIENTS WITH FIGO STAGES 1 TO 11A CERVICAL CANCER AT KENYATTA NATIONAL HOSPITAL: A COMPARATIVE CROSS-SECTIONAL STUDY

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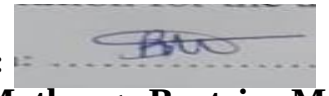
A research dissertation Submitted in Partial Fulfillment of the Requirements for the Award of the Degree in Master of Medicine in Department of Obstetrics and Gynecology, Faculty of Health Sciences, University of Nairobi.

2023

DECLARATION

I declare this dissertation is my original work and has not been submitted to any learning institution for a award of degree.

Signature:  **Date:** 7th August,2023

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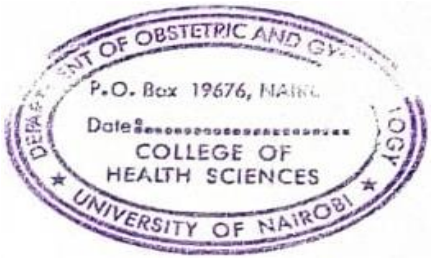

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DEDICATION

To my mother, Ann Wanjiru for her immense support during my academic journey. while undertaking this study. To my lovely daughter, Ann Blessing, and my siblings, Gladys, Faith, Danstan, and my niece Annah, for their love, encouragement, and patience.

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LIST OF ABBREVIATIONS

AC:	Adenocarcinoma
AIDS:	Acquired Immunodeficiency Syndrome
ART:	Antiretroviral therapy
CD3:	Cluster of Differentiation 3
CDC:	Centre for Disease Control
CD4:	Cluster of Differentiation 4
CIN:	Cervical Intraepithelial Neoplasia
FIGO:	International Federation for Gynecology and Obstetrics
HAART:	Highly Active Antiretroviral Therapy
HIV:	Human Immunodeficiency Virus
HPV:	Human papilloma virus
KENPHIA:	Kenya Population-based HIV Impact Assessment
LMIC:	Low- and Middle-Income Countries
LVSI:	Lymphovascular space invasion
SCC:	Squamous Cell Carcinoma
UNAIDS:	Joint United Nations Program on HIV/AIDS
WLH:	Women Living with HIV

OPERATIONAL DEFINITIONS

Cervical cancer: Malignant neoplasm that forms in the tissues of the cervix

Invasive cervical cancer: A malignant tumor that has spread from the cervix to tissue deeper in the cervix or to other parts of the body

Clinicopathological: Relating to both clinical symptoms and pathological findings on laboratory examination

Staging: The process of determining the extent to which cancer has developed by growing and spreading

Cervical intraepithelial neoplasia: A precancerous condition in which abnormal cells grow on the surface of the cervix

Papanicolaou test: A test for detecting the presence of precancerous or cancer cells on the cervix by staining the cells and observing them under a microscope

Squamous cell carcinoma: A type of cancer that begins in squamous cells

Adenocarcinoma: A type of cancer that begins in glandular cells

Adenosquamous carcinoma: A type of cancer that contains both squamous cells and glandular cells

Well-differentiated tumor: A tumor that is made up of cells that look similar to the normal

Poorly differentiated tumor: A tumor that is made up of cells that look very abnormal compared to normal cells

LIST OF TABLES

LIST OF FIGURES

TABLE OF CONTENTS

ABSTRACT

Background: Around 604,000 new cases of cancer of the cervix and 342,000 deaths from cervical cancer were reported worldwide in 2020 with human immunodeficiency virus (HIV) infections found to exacerbate its occurrence by 6.07 times. The double burden of being HIV positive and developing cancer of the cervix is a cause of concern worldwide, especially in Africa where 85% of these cases have been reported. In women living with HIV (WLH), cancer of the cervix develops among younger women, tends to be aggressive, responds poorly to treatment, and has a high rate of recurrence following treatment. In Kenya, there is limited data on cervical cancer prognosis among patients with and without HIV.

Study design/setting: Comparative cross-sectional study at Kenyatta National Hospital (KNH)

Study population: Early-stage (stage I-IIA) cervical cancer patients who were HIV positive and those who were HIV negative.

Study objective: To compare clinicopathological characteristics of women living with HIV and HIV negative women seen at Kenyatta National Hospital (KNH) from 2011 to 2021 with FIGO stages I to IIA cervical cancer.

Methodology: A comparative retrospective cross-sectional study was conducted in 2022. The hospital files of 114 cervical cancer patients living with HIV and 114 HIV-negative cervical cancer patients were retrieved from the records department. Demographic data such as age, gender, and education level; reproductive health data such as cervical cancer screening and parity; clinical data such as symptomology; and histopathology data such as cervical cancer stage, grade, histologic types, lymphovascular space invasion, and lymph node involvement were abstracted, uploaded into Statistical Package for Social Scientists (SPSS, version 25) spreadsheet and compared using Chi-square test. Logistic regression was used to adjust for demographic and reproductive factors at a 95% Confidence Interval (CI). A probability value (p-Value) of less than 0.05 was statistically significant. Odds ratios and adjusted odds ratios were interpreted as measures of effect size.

Results: The median age of cervical cancer patients who were HIV positive was significantly lower (42 years [IQR=38-49]) compared to HIV negative cervical cancer patients (47 years [40-56], p=0.011). In addition, HIV positive patients were more likely to have undergone cervical cancer screening (p=0.012), and more likely to have a higher FIGO stage (stage IIA2) compared to HIV negative women after adjusting for their age, marital status, cervical cancer screening, and age at diagnosis (AOR=7.39, (95% CI =1.53-35.7), p=0.013). Other demographic and reproductive characteristics, nodular characteristics, and lymphovascular space invasion were comparable between the groups.

Conclusions: HIV patients with cervical cancer were 5 years younger than HIV negative patients. There was no statistically significant difference in the histological type, degree of tumour differentiation, and lymph node involvement of cervical cancer between the HIV negative and positive women.

CHAPTER ONE

1 INTRODUCTION

1.1 Epidemiology of cervical cancer and HIV

Cervical cancer and HIV are major public health problems globally. Cervical cancer is the fourth leading cause of cancer-related deaths in women with 342,000 new deaths reported in 2020. Approximately, 604,000 new cases are reported every year (1,2). It accounts for half a million cases annually. The highest incidence and mortality of this preventable disease are disproportionately high in LMIC countries with Sub-Saharan Africa comprising 85% of cases and the HIV epidemic intensifies this burden. Approximately 90% of cervical cancer-induced deaths occur in underserved/poor regions of the world (2–5). In Eastern Africa, the estimated age-standardized incidence and mortality rate is high at 40.1 and 30.0 per 100,000 women (1,6). In Kenya, cancer of the cervix is the second most common malignancy after breast cancer. About 5,250 new cases are reported every year while the death rate stands at 3,286 cases. The incidence in Kenya is 20-200 per 100,000 women (7).

The prevalence of cervical cancer is significantly higher among WLH. It is categorized as an AIDS-defining malignancy together with Kaposi sarcoma and non-Hodgkin's sarcoma by CDC (8). The association between HIV and Human Papilloma Virus (HPV) infection was identified early in the HIV pandemic. HPV is a causative agent for cancer of the cervix. HIV predisposes women to a high incidence and recurrence of HPV infections and HPV-associated precancerous lesions. About 800,000 women are living with HIV in Kenya (KENPHIA 2018).

The risk of having cervical cancer is six times higher among HIV positive women compared to HIV negative women (9). They bear a huge burden of HPV-related disease and have a higher risk of death should they develop cervical cancer. Five percent of all cervical cancer cases globally are attributed to HIV positivity (10). WLH are less likely to clear HPV infections and this persistent high-risk HPV infection causes the development of cervical cancer.

Studies suggest that HIV can cause rapid progression of high-risk-HPV premalignant lesions to invasive cancer of cervix than in seronegative women by enhancing HPV carcinogenesis (11). In addition, immunosuppression seen in HIV favors persistent and recurrent HR-HPV infections with

many original research and case reports suggesting that cervical cancer in HIV positive persons is usually aggressive and of advanced nature with poor response to treatment, develops at a younger age, rapid recurrence and tend to metastasize to unusual sites. As a result, mortality among this group is rapid and the median survival is poor compared to seronegative patients (4,8,12).

This study will compare clinicopathological characteristics of HIV positive and HIV negative women treated for FIGO stages 1 to 11A cervical cancer at KNH from 2011 to 2021.

CHAPTER TWO

2 LITERATURE REVIEW

2.1 Introduction

The risk of developing cervical cancer is significantly higher among WLH. The HIV burden has seen an increase in the burden of cancer of cervix in women as well (10). In WLH, its prevalence varies widely in different countries. The areas with a high prevalence of HIV such as Africa also report a significantly higher incidence of cervical cancer yearly (4). In a meta-analysis and systematic literature search on cervical cancer risk among WLH and cervical cancer conducted by Stelzle *et al*., the risk of cervical cancer was higher in WLH, with a risk ratio of 6.07. Worldwide, cervical cancer cases among WLH increased by 5.8% in 2018. The Easter and Southern African regions are the most affected, with the prevalence of cervical cancer among WLH estimated to reach 27.4% and 63.8% respectively. The two regions contributed to 70% of the double burden of cancer of the cervix and HIV. Swaziland has the highest proportion of WLH with cervical cancer at 75% followed by Lesotho at 69% and South Africa at 63% (10).

2.2 Comparison of clinicopathologic factors of HIV positive and negative ICC patients

2.2.1 Age at diagnosis

Studies have found that cervical cancer develops at a young age among WLH women compared to HIV negative women. Progression from HPV to cervical cancer is also higher with HIV (2,3). Following HPV infection, the National Cancer Institute (NCI) estimates that it can take 15-20 years for cancer of the cervix to develop in immunocompetent persons and around 5-10 years in those with immunosuppression (5). This finding has been replicated in other published studies. In 2017, Chambuso *et al*. conducted a hospital-based study in Tanzania among women newly-diagnosed with cancer of the cervix. They found a median age of 36 years (IQR28-62) among HIV seropositive women with cervical cancer and 56 (IQR 38-81) years for HIV seronegative women with cervical cancer. Overall, WLH were 20 years younger than HIV negative women (11).

In Uganda, women living with HIV were younger with a median age of 44 years (IQR 39-48) years compared to median age of 54 years for women who were HIV negative 2019 comparative

study (13), while Abdullahi *et al*. found the peak age of presentation with cervical cancer among HIV positive women to be 30-39 years as compared to 40-49 years in HIV negative patients (12).

In Botswana, Dryden-Peterson *et al*. found that women who were living with HIV and had cervical cancer were substantially younger (median of 42 years) compared to HIV negative women (median of 57 years) (14). In Thailand, Thokanit *et al*. reported a mean age of 47 years among HIV positive patients and 54 years for HIV negative patients (6), while a retrospective study conducted by Mungo *et al* found the mean age at diagnosis to be 34 years (age range of 22-50 years) among HIV positive patients from Kisumu, Kenya (15). In conclusion, the finding of a younger age among cervical cancer patients with HIV compared to those without was consistent across these studies (5).

2.2.2 Sexual history and marital status

Human papillomavirus (HPV) is a virus that is transmitted sexually. The risk of infection is associated with a myriad of behavioral issues, key among them being having many sexual partners, early onset of sex, having high-risk sexual partners, early age at first birth, increasing parity, and history of STIs. By increasing the risk of HPV, they also increase the risk of cervical cancer (2). Cervical cancer is preventable through vaccination with the HPV vaccine and regular screening of women to identify and treat precancerous lesions (WHO 2005).

HIV positive women have a higher incidence of HPV infection and are at a higher risk of contracting HPV compared to seronegative women. In a study done by Maranga *et al* in Kenya, multiple HPV infections, including HR-HPV 52/58/68, potential HR-HPV 53/70, low-risk HPV 44,55, and abnormal cytology, were reported in smear samples of WLH compared to HIV negative women (4,8,16). In a study done by Awolude *et al*. in Ibadan in 2018 among patients with cervical cancer, most patients (73%) were married while 25% and 2 % were widowed and single respectively(17). Other studies have shown a similar pattern (6,15).

Multiparity is a risk factor for developing cervical cancer in women especially those with HPV infection (18). Previous studies done in the past show a relative risk of 3.8 to 4.4 among women with five or more births compared to nulliparous (18–20). The modal parity was 6 children with a

range of 0-14 children in research done by Awolude *et al* in Nigeria. Seventy-five percent of participants had 5 or more children. Several other studies had similar findings (8).

Early sexual debut is a risk factor for both cervical cancer and HIV. Young girls are likely to acquire the HPV virus and they are also known to have extreme sexual activities which put them at risk of STIs s including HIV (21). A study done in Brazil showed that women with earlier onset of sexual intercourse (13-16) had a higher prevalence of abnormal smears on cervical histology including LSIL and HSIL (22). The risk of acquiring HPV and cervical cancer is double among those girls whose sexual debut was at 15 years or less compared to those who started at 20 years or more. (WHO 1998).In a study done in Ibadan among patients with cervical cancer, coitarche was at a lower age among HIV positive arm at 18 years compared to 22 in the HIV negative arm (17).

Many sexual partners increase the risk of HIV and cervical cancer. Awolude *et al* found the modal lifetime sexual partners of HIV positive women to be four compared to 1 in the HIV negative arm (12). A study by Gichangi *et al*. among cervical cancer patients found that 34% reported more than two lifetime sexual partners and 37% reported that their partners had multiple sex partners (23).

2.2.3 Cervical Cancer Screening

Prevention of cervical cancer involves screening and prompt management of precancerous lesions (2). Multiple cervical screening strategies such as pap smears, visual inspection using acetic acid (VIA) or Lugol's iodine (VILI), or HPV-DNA testing are in use (2,5,7). Screening should start at 21 years of age or within the first year of onset of sexual activity among HIV positive women and be done twice in the first year after HIV diagnosis, then annually. Most WLH live in resource-limited settings where screening and treatment for cancer are not available. However, in low-resource areas such as Kenya, screening services are not readily available. In a study by Mungo *et al*., only 21% had a prior history of cervical screening, demonstrating limited screening coverage (15).

2.2.4 Diagnosis and treatment of HIV

HIV/AIDs is a predictor of cervical cancer. HIV positive women were 3.3 million in 1990. This increased to 18.8 million in 2018 - 15.5 million jumps, 60% of whom were residents of Southern

and Eastern Africa (10). The prevalence of HIV in Kenya stands at 4.9 %. Prevalence among women is 6.6%, twice that of men who stand at 3.1%.

HIV is associated with high-grade intraepithelial neoplasia (6). It also impairs the ability to clear HPV infection resulting in persistent HPV infection which in turn causes cervical intraepithelial lesions which if left untreated progress to cervical cancer (2). The Cluster of Differentiation 8 (CD8) and Cluster of differentiation 4 (CD4) T lymphocytes mediate the death of HPV-infected lesions thereby causing regression. HIV infects CD4 cells, clearing them, and causing their decline in HIV patients. Even with their increase in number following ART initiation, these CD4 cells do not recover substantially (5,14). As the CD4 count declines and HIV viral load increases, the burden of HPV infections increase and clearance of HPV reduces (8). However, cervical cancer is known to occur across all CD4 count strata (9). Women living with HIV with a normal range of CD4 count show a higher prevalence of chronic HPV infection (5).

AIDS-related mortality has declined over the years due to the use of HAART thereby increasing life expectancy nearly to the same level as HIV-negative women (23). The use of HAART has reduced the risk of having opportunistic infections, thereby improving the survival rate of patients. HIV/AIDS-related malignancies are now among the most common causes of mortality and morbidity among HIV-positive patients (5,12). Immunocompromised women have a short latency period from infection to the development of cervical cancer, usually 5-10 years, compared to 15-20 years in immunocompetent women (5). Diagnosis of cervical cancer often coincides with the diagnosis of HIV. Testing for HIV among cervical cancer patients is therefore important as it not only boosts access to treatment early but also slows the spread of HIV(23). A study by Gichangi *et al*. found the acceptability of HIV testing among cervical cancer patients at 99% (23). In another prospective study by Dryden-Peterson *et al*. in Botswana, 81% of the seropositive participants were on HAART when they were diagnosed with cancer of the cervix. 4.8 years was the median duration was Only 6.1% were started on HAART at the time of cervical cancer diagnosis (16). Mungo *et al*. had similar findings, 77% were on HAART for a mean duration of 14 months (15).

2.2.5 FIGO Stage at diagnosis

According to FIGO 2018 staging on cervical cancer, there are 4 stages. Stages 1A and 1B1 are considered early-stage cervical cancer diseases while stages 1B to 1VA are considered locally

invasive diseases. Stage 1VB is a metastatic disease with spreads beyond the true pelvis. The stage of cervical cancer influences the mode of treatment and prognosis/outcome. Wu *et al*. conducted a study in Uganda in 2019 to check the association between HIV and presentation and survival of cancer of cervix patients and found a comparable FIGO stage distribution between WLH and HIV negative women. Thirty two percent of WLH and 38% of HIV negative women presented with FIGO stage 3 or 4. After adjusting for parity, age, and transport costs to the hospital, the odds of having late-stage cervical cancer were not associated with the HIV status of patients (13).
This was comparable to the findings of a study by Abdullahi *et al*. in Nigeria that which 89% and 93% of WLH and negative patients had advanced disease (stage II B and above). Only 6% of HIV positive women presented with early disease (12).

Another study was done by Dryden-Peterson *et al* and got similar findings. Eighty percent of the patients had parametrial involvement, stages IIB, and above. These studies indicate that most patients present at an advanced stage regardless of their HIV status. These findings also compare with a descriptive study done in Ibadan by Awolude *et al*. that 93% of seropositive patients were diagnosed at a more advanced stage, FIGO stage IIB and above, compared to the HIV negative group at 63% (12). However, Mungo *et al*. found contrasting results in Kisumu Kenya among HIV patients screened for cervical cancer at a CCC clinic. Ninety three percent of patients screened had early-stage disease, stage 1A, while 3.4% had advanced disease (15). These findings could be explained by the availability of screening facilities at the clinic, which aided early diagnosis.

Human immunodeficiency virus HIV-associated immunosuppression is hypothesized to cause the severe form of cervical cancer seen in WLH. HAART is hypothesized to restore immunity and delay the progression of AIDs. However, the impact of HAART on the development and prognosis of cervical cancer is minimal (8). A comparative study in Botswana showed that even with appropriate HIV treatment, WLH who had cervical cancer had a higher risk of dying compared to seronegative women. Having HIV infection almost doubled the risk of death when a patient had cervical cancer (14). Initiation of HAART in WLH help reconstitute immunity but does not alleviate the risk of having cervical cancer. The incidence of ICC has not changed over the years even with the expansion of HAART use (5).

2.3 Comparison of histological findings of seropositive and seronegative patients with ICC

There are two main histological types. Squamous cell carcinoma is the commonest one, accounting for around 75% of all cancer cases, and is known to arise from the transformation zone of the ectocervix. Adenocarcinoma is less common and accounts for 25% of cases and is known to arise from the glandular layer of the endocervix (2). Wu *et al*. in their study in Uganda in 2019 on the relationship between having HIV and the cancer of the cervix found that squamous cell carcinoma was the most common histology in both study arms with 95% and 90% prevalence in HIV negative and positive groups respectively. Tumor differentiation was poor for the majority of the patients with 76% prevalence in seronegative group and 65% among WLH (13). This compares with a descriptive study done in Ibadan by Awolude *et al*. in 2018 that found squamous cell carcinoma to be the commonest variant in both groups, as seen in 88% of all cases. Other variants were small cell carcinoma and endometrioid adenocarcinoma. A higher proportion of adenocarcinoma was seen among WLH compared to HIV negative patients (17).

Treatment of cervical is similar irrespective of HIV status. There are no treatment guidelines for HIV patients currently (4). Three modes are mainly employed namely surgery, chemotherapy, and radiation therapy. Surgery is the first line of care for patients with early-stage ICC, while cone biopsy and radical hysterectomy/ lymph node dissection are indicated for stage 1A and stage IB to IIA respectively. Chemoradiation is indicated for cases with advanced disease. However, there are certain differences between these two groups. Treatment of precancerous lesions (CIN) among WLH increases the relapse rate of patients or risk of residual disease compared to HIV negative. Immunosuppression poses a challenge during treatment. This is worsened by chemotherapy and radiation through a reduction in CD4 count. This increases the risk of bacterial infection.

Women Living with HIV often have interruptions during treatment and record fewer cases of treatment completion (4,14). In a study done by Mungo *et al*. in Kisumu Kenya, during screening at Family AIDS Care and Education Services clinic, 93.1% of HIV patients were found to have stage $1A_1$ disease. Among them, 67% underwent LEEP, 12% had a total abdominal hysterectomy, and 20% had unknown treatment. Follow-up following LEEP at 6, 12, and 24 months revealed recurrence of disease at 8, 25, and 41 % respectively (15). This shows that HIV positive women need aggressive treatments and surveillance due to the high risk of residual disease and recurrence.

2.4 Comparison of histological grading of HIV positive and negative patients with ICC

Infection with HIV can lead to poor tumour differentiation, which leads to a poor prognosis. A study by Matovelo *et al*. in 2012 on the HIV serostatus and tumor differentiation found that HIV status and tumor differentiation were not associated. The study indicated a sixfold higher likelihood of patients with poorly differentiated tumors having HIV compared to patients who had well and moderately differentiated tumors (24). Similarly, Gichangi *et al*. found that HIV was associated with moderate to poorly differentiated histological subtypes (25). Contrary, Mbithi *et al*. study reported that the degree of tumor differentiation was comparable between the two groups (26).

2.5 Comparison of lymph node involvement between seropositive and seronegative patients with ICC

Regional lymph node spread is a major route of the spread of cervical cancer. Lymph node metastasis helps determine the need for adjuvant treatment after surgery and is a predictor of recurrence and death (27). The risk of metastasis of early-stage cervical cancer to lymph nodes is 15%-20%. The incidence of nodal metastasis increases with the clinical FIGO stage. The increasing depth of stromal invasion increases the risk of lymph node metastasis (27). Other factors include lymphovascular space invasion, SCC-antigen concentration, and maximum tumor diameter. There is a need to add chemoradiation to the treatment plan when post-operative examination reveals lymph node metastasis. This helps prevent recurrence and death from early cervical disease (28). Carrie *et al* found a similar presentation and nodal characteristics between WLH and HIV negative cervical cancer patients on Positron emission tomography (29).

2.6 Comparison of lymphovascular space invasion between HIV positive and negative patients with ICC

Lymphovascular space invasion is the existence of cancer cells in the vessels and lymphatics and is a sign of cancer spread. Lymphovascular space invasion is a better indicator of lymph node disease compared to lymph node status. It is normally present when tumor cells found in luminal spaces have an endothelial cell lining after hematoxylin and eosin staining. The involvement of vascular and lymphatic spaces does not change the staging. Lymphovascular invasion is an unfavorable prognostic factor in cervical cancer and is often an indicator of local recurrence and

distant metastasis after surgical treatment of early cervical cancer disease. Morice *et al* in a study done on the prognostic value of LVSI found that 45% of patients who had surgical intervention for early-stage cervical cancer had LVSI (30). Adjuvant therapy is needed if LVSI is present following surgery.

2.7 Study Justification

Cervical cancer is the commonest gynecological cancer in Kenya. Its incidence is high among WLH. This AIDS-defining malignancy is also more likely to be diagnosed with a concurrent HPV infection which is a causative agent for cancer. HIV has been shown to change the clinical characteristics of cervical cancer. Among WLH, cervical cancer has been seen to develop at a younger age, is normally aggressive with poor response to treatment, and is prone to recurring following treatment. Studies have also found that WLH are at risk of developing precancerous lesions, which rapidly progress to cervical cancer.

The prevalence of cancer of the cervix is directly linked with the burden of the HIV/AIDS pandemic which is highest in Sub-Saharan region. In Kenya, HIV/AIDS afflicts 6.6% of adult women. Its incidence has changed over the years with more cases diagnosed at a young age which may be due to HPV acquired at a young age or HIV/HPV co-infection. There are limited studies in Kenya looking at the effect of HIV on clinicopathological characteristics in cervical cancer patients.

This study compared the differences in clinicopathological characteristics between patients with FIGO stages 1 to IIA cancer of the cervix who were seropositive compared to those who are seronegative. This knowledge will be used to inform clinical practice for this high-risk group. The findings of this study will provide more insight useful in the development of health education and sensitization programs on cervical cancer and screening programs.

2.8 Conceptual framework

2.8.1 Narrative

The high number of cases of cancer of the cervix is a concern globally, with 85% of the cases emanating from Sub-Saharan Africa. Presence of HIV is a significant risk factor for cancer of the

cervix.The risk of developing cancer of cervix is estimated to be six times more among WLH than HIV negative women. In addition, early sexual debut, having many sexual partners, and having high-risk sexual partners are other associated factors. Cervical cancer is considered to be a comorbidity of HIV and AIDS-defining cancer. Invasive cervical cancer among seropositive women is a major public health problem in Kenya.

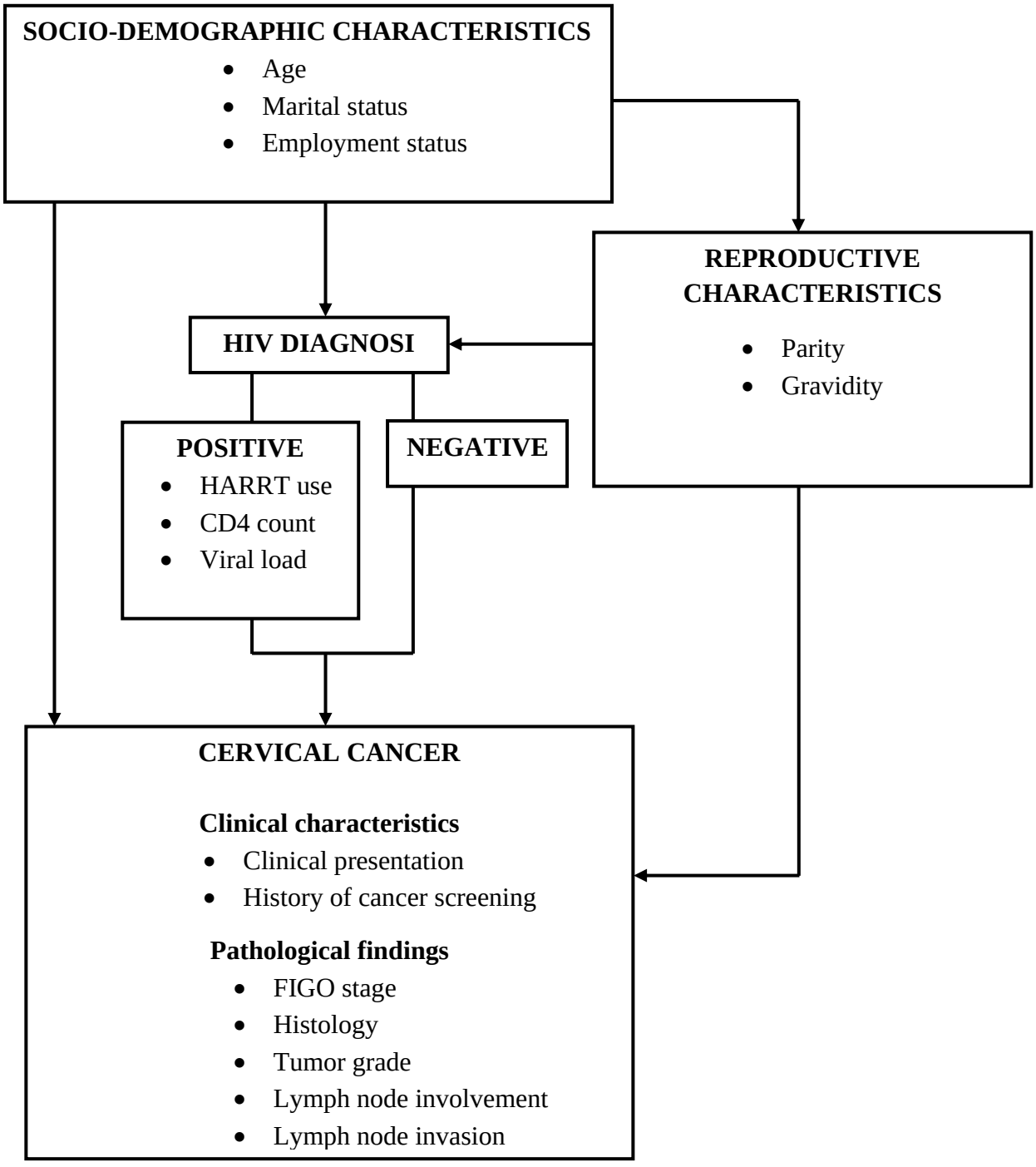


Figure 2.1. Conceptual framework

2.9 Research question

Are there differences in clinicopathological characteristics of HIV positive and HIV negative women with FIGO stages 1 to 11A cancer of the cervix seen at KNH between 2011 and 2021?

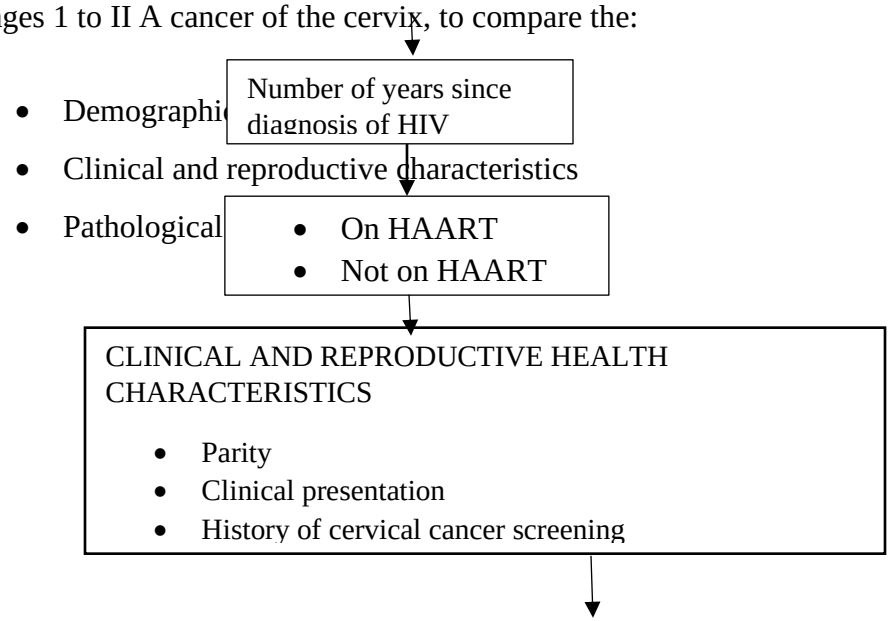
2.10 Objectives

2.10.1 Broad Objective

To compare the clinicopathological characteristics of HIV positive and negative women with FIGO stages 1 to IIA cancer of the cervix seen at KNH between 2011 and 2021.

2.10.2 Specific objectives

Among HIV positive and HIV negative women seen at KNH between 2011 and 2021 with FIGO stages 1 to II A cancer of the cervix, to compare the:



CHAPTER THREE

3 METHODOLOGY

3.1 Study design

A retrospective comparative cross-sectional study was conducted. The demographic, clinical, reproductive, and pathological findings of women living with HIV and cervical cancer FIGO stage 1 to IIA were compared with those of HIV negative women with similar FIGO stages.

3.2 Study setting

The study site was Kenyatta National Hospital, which is the main referral and public health facility in Kenya. It is located in the west of Upper hill in Nairobi and offers both preventive and curative services for various illnesses and has a bed capacity of 1800. It receives patients from Kenya and the East African region and is the largest government hospital that offers cancer treatment in the country, providing chemotherapy, surgery, and radiotherapy services for cancer patients. Files of patients who have received cervical cancer treatment at KNH were gotten from the records department and data was extracted. The main outpatient gynae-oncology clinic is conducted in clinic 18 where new patients or patients on follow-up after completion of cancer treatment are seen. On average, 80 patients with cancer of the cervix are seen every month.

The main inpatient ward is 1D where patients with acute complications like anemia, sepsis, venous thrombosis, and renal failure are admitted. On average 20 patients with cancer of the cervix are admitted every month. Patients who require surgery are admitted to ward 1B. In addition, around 40 patients per day receive radiotherapy sessions at the radiotherapy department.

3.3 Study population

These were patients who received cervical cancer treatment at KNH from 2011 to 2021 with FIGO stages 1 to 11A. Secondary data from hospital files were used. Therefore, only patients with archived and complete medical information qualified for the study.

3.3.1 Inclusion criteria

- Histologically diagnosed cervical cancer

- FIGO stages 1A,1B and IIA
- Known HIV status

3.3.2 Exclusion criteria

- Patients with missing critical information (histology findings)

3.4 Sample size calculation

In a descriptive study of seropositive and seronegative women with ICC who presented for clinical staging at Ibadan, Nigeria, 18.8% of WLH and 6.0% of HIV-negative women were diagnosed with adenocarcinoma. These findings were used to calculate sample size (n) with a statistical power of 0.8, alpha of 0.05, and a beta of 0.2 as shown below.

Statistical formula and computation (Rosnar, 2011)

$$N_1 = \left\{ z_{1-\alpha/2} * \sqrt{\bar{p} * \bar{q} * (1 + \frac{1}{k})} + z_{1-\beta} * \sqrt{p_1 * q_1 + (\frac{p_2 * q_2}{k})} \right\}^2 / \Delta^2$$

$$q_1 = 1 - p_1$$

$$q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + kp_2}{1 + K}$$

$$\bar{q} = 1 - \bar{p}$$

$$N_1 = \left\{ 1.96 * \sqrt{0.124 * 0.876 * (1 + \frac{1}{1})} + 0.84 * \sqrt{0.188 * 0.812 + (\frac{0.06 * 0.94}{1})} \right\}^2 / 0.128^2$$

$$N_1 = 103$$

$$N_2 = K * N_1 = 103$$

Definitions

P1, P2 = proportion of adenocarcinoma among HIV positive (P1) and HIV negative (P2)

Δ = absolute difference between proportions (P2-P1)

n1 = sample size for HIV positive women

n2 = sample size for HIV negative women

α = probability of having type 1 error (0.05)

β = probability of having type II error (0.2)

z = critical Z value for α or β

K = ratio of sample size for HIV positive and HIV negative

We required 103 seropositive women treated for cervical cancer and 103 HIV negative patients treated for cervical cancer. After a 10% markup to cover missing data, 114 HIV positive women treated for cervical cancer and 114 HIV negative patients treated for cervical cancer were required.

3.5 Sampling procedure

Consecutive sampling was used to recruit participants. Files were retrieved from hospital archives, checked for completeness, and qualified recruited until the sample size was reached.

3.6 Data variables

Table 3.1. Data variables

Objective	**Variable**	**Source of data**
1. Sociodemographic characteristic of FIGO stages 1 to IIA cervical cancer patients with and without HIV	• Age • Marital status • Education level • Employment status	Patient's files
2. Clinical and reproductive health characteristics	• Parity • Age at diagnosis of cancer • Prior cervical cancer Screening • Clinical presentation • CD4 count • Viral load	Patient's files
2. To compare the FIGO stage on diagnosis among cervical cancer patients with HIV and those who are HIV negative	• FIGO stage at diagnosis • Histopathology • Grade of the tumour • Involvement of lymph nodes • Invasion of lymphovascular space	Patient's files

3.7 Data collection

3.7.1 Study tool

A data abstraction tool was used to record secondary data. The data recorded in the tool was age, level of education, marital status, and status of employment, and reproductive data such as parity, history of cervical cancer screening, and age at cervical cancer diagnosis. The tool was also used to record medical data on HIV status, use of HAART, CD4 count, viral load, and period of treatment, and data on pathological findings such as FIGO stage of cancer at diagnosis, histopathology, lymphovascular space invasion, tumor grade, and lymph node involvement.

Construct validation (31) was used to ascertain the validity of the questionnaire. Briefly, only questions that recorded the sociodemographic, reproductive, and medical data of patients such as cervical cancer histopathology and clinical characteristics of patients were used. Indicators were guided by existing knowledge and questionnaires shared with supervisors and the ethics review committee for review. After review, the tool was revised to ensure accurate data collection.

3.7.2 Data collection procedure

Information was abstracted from the patients' files and recorded in the study tool. Demographic characteristics such as age, gender, HIV diagnosis, and relationship status were abstracted and recorded. Medical data such as stage of cancer, lymphovascular space invasion, tumor grade, and lymph node involvement were also abstracted from hospital files and recorded in the study tool.

3.7.3 Data quality assurance

Qualified personnel, which included one research assistant and the Principal Investigator (PI), collected the data. The research assistant was trained on research ethics, data collection, and data management before deployment. The PI checked the filled study tools before submission for analysis. The study tool was checked for completeness and clarifications were sought, if necessary, before filing and submission to a qualified statistician for data analysis.

3.8 Data analysis

Study tools were reviewed, data extracted, and data uploaded and cleaned using version 25 of the Statistical Package for Social Scientists (SPSS) software. The analysis was done as follows:

Table 3.2. Data analysis per objective

Objective	Analysis procedure
Sociodemographic characteristics of FIGO stages 1A,1B, and IIA cervical cancer patients with and without HIV	• Chi-square test was used to compare the sociodemographic data. The confidence interval was set at 95%. The associations were to be significant if P-value is <0.05.
To compare clinical and reproductive health characteristics among patient among cervical cancer patients with HIV and those who are negative	• Clinical characteristics such as parity, cancer screening in the past, age at cervical cancer diagnosis, history of cervical cancer screening, and symptoms of patients with cancer of the cervix with HIV were compared with those of cervical cancer patients who were seronegative using the Chi-square test. Odds ratios were the measures of effect size. • A probability value less than 0.05 was to be significant. • Potential confounders were controlled using logistical regression.
Pathological findings of cervical cancer patients with HIV and those who are HIV negative	• Pathologic findings such as FIGO stage on diagnosis, histologic types, and grade, invasion of lymphovascular space, and involvement of lymph nodes among cervical cancer patients with HIV were compared with those cervical cancer patients who are seronegative using the Chi-square test. • Odds ratios were to be the measures of effect size. • Logistic regression was used to control confounders.

3.9 Ethical considerations

3.9.1 Study approvals

Authorization was sought from KNH and the Ethics and Review Committee (ERC) of the University of Nairobi before conducting the study. The study tools and protocols were submitted for review and only approved materials were used in the definitive study. Authorization to conduct this study was also sought from the Obstetrics and Gynecology department of the University of

Nairobi and the Kenyatta National Hospital administration before accessing files and collecting data.

3.9.2 Confidentiality

The confidentiality of participants was upheld during and after the study. Personal identifiers such as names, national identification numbers, and hospital file numbers were not recorded in the questionnaires. Instead, participants were identified using study-generated numbers, which were not shared during the presentation or dissemination of results. Secondary data was used.

3.10 Study closure procedure

Unused research tools, including questionnaires and consent forms, were collected and filed. Filled questionnaires were also filed and stored in a locked cabinet at KNH for safe storage for at least 10 years. Finally, a study closure letter was drafted and submitted to KNH/UON ERC.

3.11 Results dissemination procedures

The results were compiled in a thesis, which was submitted to the University of Nairobi, department of Obstetrics and gynaecology. A manuscript was written and published in a peer-reviewed journal of medicine. Data will also be presented at conferences.

CHAPTER FOUR

4 RESULTS

One thousand two hundred and sixty (1260) hospital files of cervical cancer patients were retrieved and reviewed. One thousand and thirty-two of these were excluded either for not meeting the inclusion criteria (n=924) or having over 50% missing data (n=108). In the end, 228 participants were recruited, 114 being seropositive cervical cancer patients and 114 seronegative patients.

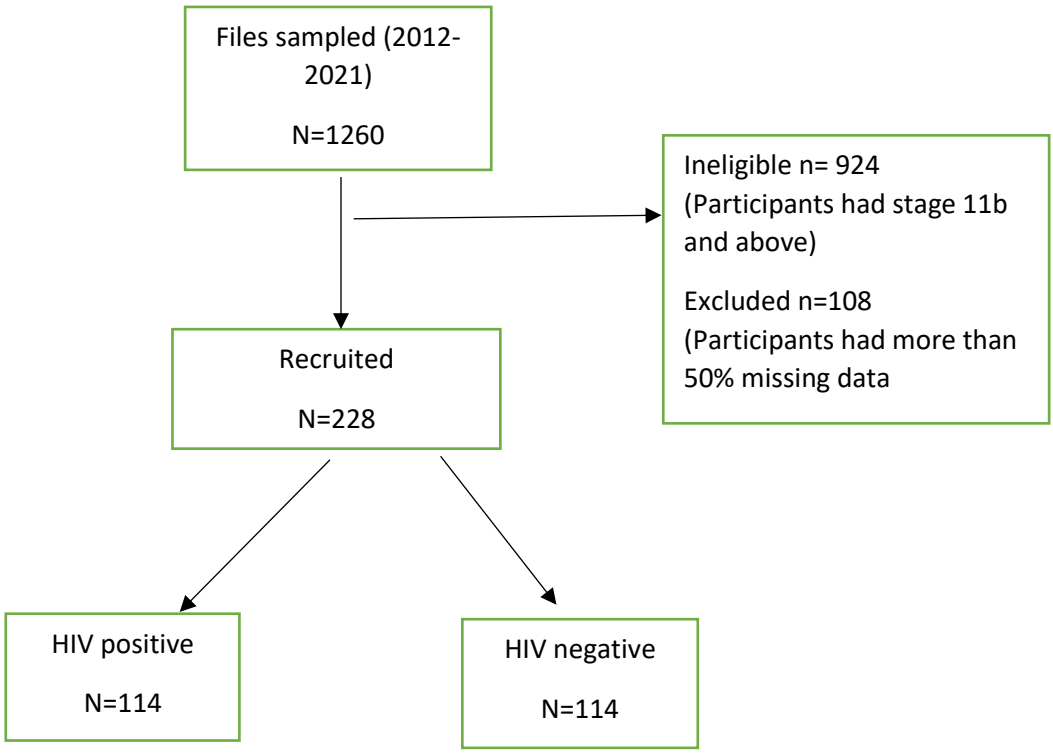


Figure 4.1. Recruitment schema of study participants

The data of the 114 cervical cancer patients living with HIV and the 114 cervical cancer patients seronegative were reviewed and abstracted from hospital files. The comparisons of their demographic, reproductive, clinical, and pathological characteristics are presented below.

4.1 Demographic characteristics

Table 4.1 below shows the comparison of demographic factors of HIV positive and negative women with FIGO stages (I-IIA) cervical cancer seen at Kenyatta National Hospital in 2011-2021.

The median age of seropositive patients with cervical cancer was significantly lower at 42 years [IQR=38-49] compared to the age seronegative cervical cancer patients at 47 years [IQR=40-56], p=0.011. Other demographic factors such as education level, marital status, employment status, or religion were comparable.

Table 4.1. Demographic characteristics of HIV positive compared to HIV negative patients with FIGO stages (I-IIA) cervical cancer at KNH in 2011-2021

	HIV status			
	Positive	**Negative**	**OR (95% CI)**	**p-Value**
Median age [IQR]	42 [38-49]	47 [40-56]	-	**0.011**
Marital status				
Married	71 (47.7)	78 (52.3)	Reference	
Single	20 (52.6)	18 (47.4)	1.22 (0.58-2.41)	0.584
Widowed	10 (43.5)	13 (56.5)	0.85 (0.34-2.12)	0.709
Divorced/separated	13 (72.2)	5 (27.8)	2.86 (0.99-7.51)	0.05
Education level				
No formal education	7 (41.2)	10 (58.8)	0.70 (0.18-2.46)	0.583
Primary	59 (50.0)	59 (50.0)	1.00 (0.41-2.46)	1.000
Secondary	37 (52.1)	34 (47.9)	1.09 (0.40-2.93)	0.863
Tertiary	11 (50.0)	11 (50.0)	Reference	
Employment status				
Employed	14 (70.0)	6 (30.0)	Reference	
Self employed	34 (49.3)	35 (50.7)	0.42 (0.14-1.22)	0.102
Unemployed	66 (47.5)	73 (52.5)	0.39 (0.14-1.01)	0.059
Religion				
Christian	109 (49.1)	113 (50.9)	Reference	
Muslim	5 (83.3)	1 (16.7)	5.18 (0.69-61.6)	0.213

4.2 Reproductive and clinical characteristics

Table 4.2 shows the comparison of reproductive and clinical factors of HIV positive and negative women with FIGO stages (I-IIA) cervical cancer at KNH in 2011-2021. Cervical cancer patients who were living with HIV were 2.04 times (95% CI=1.17-3.52) likely to have undergone screening for cervical cancer compared to seronegative women (p=0.012). The proportion of HIV positive patients who presented with dyspareunia, vaginal bleeding, per vaginal discharge, hematuria, lower abdominal pain, and painful defecation was comparable with that of seronegative women. Treatment modalities for seropositive and seronegative patients were comparable. However, among the patients who underwent radiotherapy, median radiotherapy cycles were significantly lower among HIV positive [23 (10-25)] compared to HIV negative [25 (23-25)] participants diagnosed with cervical cancer (p=0.036). Median chemotherapy cycles and surgical interventions provided were comparable.

The majority of HIV patients were on antiretroviral drugs (93.0%), mostly for less than five years (38.5%), and had not undergone CD4 testing (61.4%). Only 17 (14.9%) had undergone CD4

testing, the majority of whom were found to have an undetectable (≤50 copies/mL) viral load (76.5%).

Table 4.2. Reproductive and clinical characteristics of HIV positive compared to HIV negative patients with FIGO (I-IIA) cervical cancer at KNH from 2011 to 2021

	HIV status			
	Positive	**Negative**	**OR (95% CI)**	**p-Value**
Parity				
Nulliparous	4 (80.0)	1 (20.0)	4.24 (0.67-52.6)	0.209
Primiparous (1)	9 (75.0)	3 (25.0)	3.18 (0.81-11.2)	0.129
Multiparous (2-4)	66 (48.5)	70 (51.5)	Reference	
Grandmultiparous (>5)	35 (47.3)	39 (52.7)	0.95 (0.55-1.71)	0.864
Not reported	0	1		
Cervical cancer screening				
Yes	48 (61.5)	30 (38.5)	2.04 (1.17-3.52)	**0.012**
No	66 (44.0)	84 (56.0)	Reference	
Symptomatology				
Asymptomatic	4 (40.0)	6 (60.0)	Reference	
Symptomatic	110 (50.5)	108 (49.5)	1.53 (0.39-4.89)	0.748
Symptoms				
Dyspareunia	18 (43.9)	23 (56.1)	0.72 (0.36-1.41)	0.351
Per vaginal bleeding	96 (50.5)	94 (49.5)	1.02 (0.48-2.19)	0.959
Per vaginal discharge	80 (54.1)	68 (45.9)	1.57 (0.87-2.78)	0.123
Post coital bleeding	6 (37.5)	10 (62.5)	0.57 (0.19-1.49)	0.202
Hematuria	3 (50.0)	3 (50.0)	0.98 (0.23-4.28)	1.000
LAPS	1 (33.3)	2 (66.7)	0.49 (0.03-4.24)	0.619
Painful defecation	1 (50.0)	1 950.0)	0.98 (0.05-18.8)	1.000
Foul smell	2 (100)	0 (0.0)	-	-
Leakage of urine	0 (0.0)	1 (100)	-	-
Back pain	0 (0.0)	3 (100)	-	-
Abdominal pain	1 (100)	0 (0.0)	-	-
Treatment modalities				
Chemotherapy	5 (55.6)	4 (44.4)	0.88 (0.19-3.27)	1.000
Radiotherapy	21 (72.4)	8 (27.6)	1.84 (0.66-5.13)	0.259
Surgery	68 (43.9)	87 (56.1)	0.55 (0.27-1.13)	0.113
Combined treatment	20 (58.8)	14 (41.2)	Reference	
Herbal medicine	0 (0.0)	1 (100)	-	-
Chemotherapy cycles	3.0 [1.5-3.0]	3.0 [2-6]	-	0.789
Radiotherapy cycles	23 [10-25]	25 [23-25]	-	**0.036**
Type of surgery				
Radial hysterectomy	85 (57.4)	63 (42.6)	2.69 (0.31-39.5)	0.578

TAH	1 (33.3)	2 (66.7)	Reference	
Cervical cone biopsy	0 (0.0)	1 (100)	-	-

4.3 Pathological characteristics

Inferential and multivariable statistics were used to compare the pathological characteristics of WLH and HIV negative women who were diagnosed with FIGO stages (I-IIA) cervical cancer at KNH between 2011 and 2021 (Table 4.3). After adjusting for demographic and reproductive factors such as the age of participants, age at cervical cancer diagnosis, marital status, and history of cervical cancer screening, the adjusted odds of having stage IIA2 cervical cancer was 7.39-fold (95% CI=1.53-35.7) higher among the WLH compared to HIV negative women (p=0.013). Moreover, cervical cancer patients who were seropositive compared to seronegative women were 1.32 times (95% CI=0.54-3.23) more likely to have squamous carcinoma than other histological types and 1.58 times (95% CI=0.67-3.74) more likely to have lymph node involvement but differences were not statistically significant. The adjusted odds of having poorly differentiated tumors and having lymphovascular space involvement were 0.30 times (95% CI=0.09-1.02) and 0.86 times (95% CI=0.36-2.07) lower among seropositive patients compared to seronegative patients.However, the differences were not statistically significant.

Table 4.3. Pathological characteristics of HIV positive compared to HIV negative patients with early-stage (I-IIA) cervical cancer at KNH from 2011 to 2021

	HIV status					
	Positive	**Negative**	**OR (95% CI)**	**p-Value**	**AOR (95% CI)**	**p-Value**
FIGO stage at diagnosis						
IA1	4 (40.0)	6 (60.0)	Reference			
IA2	4 (50.0)	4 (20.0)	1.50 (0.24-11.0)	1.000	1.38 (0.18-10.5)	0.754
IB1	17 (39.5)	26 (60.5)	0.98 (0.28-3.45)	1.000	1.43 (0.29-6.89)	0.657
IB2	14 (34.1)	27 (65.9)	0.78 (0.22-2.78)	0.727	1.42 (0.29-6.96)	0.666
IB3	5 (41.7)	7 (58.3)	1.07 (0.23-5.24)	1.000	2.33 (0.35-15.6)	0.385
IIA1	21 (48.8)	22 (51.2)	1.43 (0.40-4.97)	0.732	3.38 (0.67-17.0)	0.140
IIA2	49 (69.0)	22 (31.0)	3.34 (0.92-11.2)	0.086	7.39 (1.53-35.7)	**0.013**
Histopathology						
Adenocarcinoma	11 (37.9)	18 (62.1)	Reference			
Adenosquamous carcinoma	1 (100)	0 (0.0)	-	-	-	-
Squamous carcinoma	102 (51.5)	96 (48.5)	1.74 (0.78-3.77)	0.172	1.32 (0.54-3.23)	0.541
Grading						
Poorly differentiated	18 (39.1)	28 (60.9)	0.30 (0.11-0.92)	**0.025**	0.30 (0.09-1.02)	0.054
Moderately differentiated	81 (50.6)	79 (49.4)	0.48 (0.19-1.26)	0.122		

Well-differentiated	15 (68.2)	7 (31.8)	Reference			
Lymph node involvement						
Present	22 (66.7)	11 (33.3)	2.22 (1.06-4.91)	**0.041**	1.58 (0.67-3.74)	0.301
Absent	92 (47.4)	102 (52.6)	Reference			
Not reported	0	1				
Lymphovascular space involvement						
Present	13 (46.4)	15 (53.6)	0.84 (0.38-1.79)	0.668	0.86 (0.36-2.07)	0.742
Absent	101 (50.8)	98 (49.2)	Reference			
Not reported	0	1				

CHAPTER FIVE

5 DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

5.1 Discussion

A comparative cross-sectional study was conducted at Kenyatta National Hospital in 2022 to compare the clinicopathological characteristics of seropositive patients with cervical cancer and those who were seronegative. From the data, demographic characteristics were comparable, apart from age, which was significantly lower among women who were HIV negative compared to women who were seronegative. Moreover, WLH were more likely to have undergone screening for cervical cancer compared seronegative women.

Cervical cancer patients who were seropositive were more likely to be younger (Median=42 years [38-49]) compared to women who were HIV negative (Median=47 years [40-56]) with the difference found to be statistically significant. This finding is similar to the findings of other authors, which have been published from other regions in Africa and the developed world. In a 2017 hospital-based study by Chambuso *et al*. in Tanzania, for instance, positive women who were newly diagnosed with cancer of the cervix were more likely to be younger (Median=36 years (IQR=28-62)) compared to HIV negative women (Median=56 years (IQR 38-81) years (11). In Uganda, in a study by Wu et al., women living with HIV were approximately 10 years younger than HIV negative women in a 2019 comparative study (13), while Abdullahi *et al*. found the peak age of presentation with cervical cancer among HIV positive women to be 30-39 years as compared to 40-49 years in HIV negative patients (12). Studies in In Botswana (14), Thailand (6), and Kisumu, Kenya (15) have also reported similar findings. This shows and affirms that HIV positive women may develop cancer of the cervix at an earlier age compared to HIV negative women. According to the National Cancer Institute (NCI), it can take around 15-20 years for cancer of the cervix to develop in immunocompetent individuals and approximately 5-10 years in HIV positive women (5).

Other factors such as the educational level of the participants, the employment status of patients, marital status, and the religion of the patients were comparable between the two groups.

Clinical characteristics of cervical cancer patients who were seropositive and those who were seronegative were compared using inferential statistics. The data showed a positive and

statistically significant relationship between HIV status and screening for cancer of the cervix. In general, the odds of cervical cancer screening was 2.04-fold higher among patients who were living with HIV compared to those who were HIV negative – a common finding in the literature. This may be attributable to the many contacts with healthcare workers as they go to get ARVs.WLH should be screened regularly for cervical cancer due to the increased risk.

Symptoms of cancer of the cervix were comparable between HIV positive and HIV negative patients with cancer of the cervix. Prevalence dyspareunia, per vaginal discharge, vaginal bleeding, and postcoital bleeding were comparable.

The pathological characteristics of patients who were living with HIV with cancer of the cervix were mostly comparable with those of women who were HIV negative, apart from the FIGO stage, which was higher among seropositive women. Multivariable analysis showed that WLH were more likely to present with an advanced FIGO stage after controlling for demographic factors such as age and marital status and clinical data such as age at cervical cancer diagnosis. From the data, cervical cancer patients who were HIV positive were 7.39 times more likely to have stage IIA2 cervical cancer compared to cervical cancer patients who were HIV negative. However, the tumor grade and the frequency of patients who had lymph node involvement, and those who had lymphovascular space invasion among HIV positive patients were comparable to cervical cancer patients who were HIV negative. Even though most published studies support this narrative, deviant results have also been reported. In Nigeria, studies by Abdullahi *et al*. (12) and Dryden-Peterson *et al.* (12) reported a positive and statistically significant correlation between the severity of HIV seropositivity and the severity of cervical cancer. In Uganda, the severity of cervical cancer was not correlated with HIV seropositivity in a 2019 study by Wu *et al*. (13), while a study in Kisumu, Kenya found a positive, statistically significant correlation between HIV status and the odds of having early-stage cervical cancer (15). Differences in population and the availability of screening facilities in HIV endemic areas such as Kisumu could explain the variances in the results that have been reported in the literature. Also, even though HIV-linked immunosuppression is hypothesized to contribute to the aggressive nature of cervical cancer seen in women living with HIV, HAART has been shown to restore immunity, delay progression to AIDs, and slow down the progression of cervical cancer albeit marginally (8). The nodular characteristics and lymphovascular space invasion are similar among cervical cancer patients with and without HIV (29,30), thereby supporting our findings.

5.2 Conclusion

- Women who are seropositive are more likely to develop cancer of the cervix at a younger age compared to women who are seronegative.
- HIV seropositive patients are more likely to develop higher FIGO stage disease compared to HIV negative women.
- The histological type, tumour differentiation, lymph node involvement, and probability of having lymphovascular space invasion was comparable between the two groups.

5.3 Recommendations

All women should undergo regular cervical cancer screening regardless of their HIV status.

REFERENCES

1. Cancer IA for R on, Organization WH. 7 794 798 844. Globocan 2020. 2020;419:1–2.
2. LaVigne K, Leitao MM. Cervical cancer prevention. Fundamentals of Cancer Prevention: Fourth edition. 2019;629–52.
3. Jedy-Agba E, Joko WY, Liu B, Buziba NG, Borok M, Korir A, et al. Trends in cervical cancer incidence in sub-Saharan Africa. British Journal of Cancer. 2020;123(1):148–54.
4. Ntekim A, Campbell O, Rothenbacher D. Optimal management of cervical cancer in HIV-positive patients: A systematic review. Cancer Medicine. 2015;4(9):1381–93.
5. Ghebre RG, Grover S, Xu MJ, Chuang LT, Simonds H. Cervical cancer control in HIV-infected women: Past, present, and future. Gynecologic Oncology Reports. 2017;21(June):101–8.
6. Thokanit NS, Kosalaraksa P, Jitkasikorn P, Thonkamdee T, Promchana S, Wilailak S. A prognostic study of patients with cervical cancer and HIV/AIDS in Bangkok, Thailand. Gynecologic Oncology Reports. 2020;34:100669.
7. Ministry of Health K. 2 | Kenya National Cancer Screening Guidelines | 3. WwwHealthGoKe. 2019;2–122.
8. Blattner WA, Nowak RG. Encyclopedia of AIDS. Encyclopedia of AIDS. 2016;1–12.
9. Godfrey C, Prainito A, Lapidos-Salaiz I, Barnhart M, Watts DH. Reducing cervical cancer deaths in women living with HIV: PEPFAR and the Go Further partnership. Preventive medicine. 2021;144(March):106295.
10. Stelzle D, Tanaka LF, Lee KK, Ibrahim Khalil A, Baussano I, Shah AS V, et al. Estimates of the global burden of cervical cancer associated with HIV. The Lancet Global Health. 2021 Feb;9(2):e161–9.
11. Chambuso RS, Kaambo E, Stephan S. Observed Age Difference and Clinical Characteristics of Invasive Cervical Cancer Patients in Tanzania; A Comparison between HIV-Positive and HIV-Negative Women. Journal of Neoplasm. 2017;02(03):1–5.
12. Abdullahi A, Mustapha MI, David DA, Ayodeji OT. Human immunodeficiency virus seroprevalence in patients with invasive cervical cancer in Zaria, North-Western Nigeria.

Annals of African Medicine. 2018;17(1):17–21.

13. Wu ES, Urban RR, Krantz EM, Mugisha NM, Nakisige C, Schwartz SM, et al. The association between HIV infection and cervical cancer presentation and survival in Uganda. Gynecologic Oncology Reports. 2020;31:100516.

14. Dryden-Peterson S, Bvochora-Nsingo M, Suneja G, Efstathiou JA, Grover S, Chiyapo S, et al. HIV infection and survival among women with cervical cancer. Journal of Clinical Oncology. 2016;34(31):3749–57.

15. Mungo C, Cohen CR, Maloba M, Bukusi EA, Huchko MJ. International Journal of Gynecology and Obstetrics Prevalence, characteristics, and outcomes of HIV-positive women diagnosed with invasive cancer of the cervix in Kenya. International Journal of Gynecology and Obstetrics. 2013;123(3):231–5.

16. Maranga IO. HIV Infection Alters the Spectrum of HPV Subtypes Found in Cervical Smears and Carcinomas from Kenyan Women. The Open Virology Journal. 2013;7(1):19–27.

17. Awolude OA, Oyerinde SO. Invasive cervical cancer in Ibadan: Socio-sexual characteristics, clinical stage at presentation, histopathology distributions and HIV status. African Journal of Infectious Diseases. 2019;13(1):32–8.

18. Hinkula M, Pukkala E, Kyyrönen P, Laukkanen P, Koskela P, Paavonen J, et al. A population-based study on the risk of cervical cancer and cervical intraepithelial neoplasia among grand multiparous women in Finland. British Journal of Cancer. 2004;90(5):1025–9.

19. Gichangi P, De Vuyst H, Estambale B, Rogo K, Bwayo J, Temmerman M. HIV and cervical cancer in Kenya. International Journal of Gynecology and Obstetrics. 2002;76(1):55–63.

20. Munoz N, Franceschi S, Bosetti C, Moreno V, Herrero R, Smith JS, et al. Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. TT - [Rôle de la parité et du papillomavirus humain dans le cancer du col de l'utérus : étude multi-centrée de contrôle de cas de l'IARC]; [Papel de la. Lancet. 2002;359(9312):1093–101.

21. Sulistyawati D, Faizah Z, Kurniawati EM. An Association Study of Cervical Cancer Correlated with The Age of Coitarche in Dr. Soetomo Hospital Surabaya. Indonesian Journal of Cancer. 2020;14(1):3.

22. Cândido J, Xavier-Júnior C, Dufloth RM, Bhadra Vale D, Tavares De Lima M, Zeferino LC. Early Age at First Sexual Intercourse is Associated with Higher Prevalence of High-grade Squamous Intraepithelial Lesions (HSIL) Idade precoce de início da atividade sexual está associada a elevada prevalência de Lesão Intraepitelial Escamosa de Alto Grau. Rev Bras Ginecol Obstet. 2017;39:80–5.

23. Gichangi P, Estambale B, Bwayo J, Rogo K, Ojwang S, Njuguna E, et al. Acceptability of human immunodeficiency virus testing in patients with invasive cervical cancer in Kenya. International Journal of Gynecological Cancer. 2006;16(2):681–5.

24. Matovelo D, Magoma M, Rambau P, Massinde A, Masalu N. HIV serostatus and tumor differentiation among patients with cervical cancer at Bugando Medical Centre. BMC Research Notes. 2012;5:1–8.

25. Gichangi PB, Bwayo J, Estambale B, De Vuyst H, Ojwang S, Rogo K, *et al*. Impact of HIV infection on invasive cervical cancer in Kenyan women. Aids. 2003;17(13):1963–8.

26. Clinicopathologic Findings Of Cervical Cancer Among Hiv Negative And Positive Patients Seen At Moi Teaching And Referral Hospital BY. 2015;

27. Hospital U. Progress in the Study of Lymph Node Metastasis in Early-stage Cervical. 2018;38(4).

28. Wu C, Li L, Xiao X, Sun A, Lin W, Li A. Risk factors of regional lymph node metastasis in patients with cervical cancer. 2019;208–13.

29. Minnaar CA, Baeyens A, Ayeni OA, Kotzen JA, Vangu M. Defining Characteristics of Nodal Disease on PET / CT Scans in Patients With HIV-Positive and -Negative Locally Advanced Cervical Cancer in South Africa. 2019;5(4):339–45.

30. Morice P, Piovesan P, Rey A, Atallah D, Haie-Meder C, Pautier P, et al. Prognostic value of lymphovascular space invasion determined with hematoxylin-eosin staining in early-stage cervical carcinoma: Results of a multivariate analysis. Annals of Oncology. 2003;14(10):1511–7.

31. Peter JP. Construct Validity: A Review of Basic Issues and Marketing Practices. Journal of Marketing Research. 1981 May 28;18(2):133–45.

APPENDICES

Appendix 1. Questionnaire

CLINICOPATHOLOGICAL CHARACTERISTICS OF HIV POSITIVE AND HIV NEGATIVE PATIENTS WITH FIGO STAGES 1 TO 11A CERVICAL CANCER AT KENYATTA NATIONAL HOSPITAL

(Fill all sections)

Study number …….. Date……

Demographic characteristics

1. What is the patient's age in years? …….

2. What is the patient's marital status? *(tick one)*

☐Married ☐Single ☐Divorced/separated ☐Widowed

3. What is the highest education level? *(tick one)*

☐Primary ☐Secondary ☐Tertiary

4. What is the patient's employment status? *(tick one)*

☐Employed ☐Unemployed ☐Student

5. What is the patient's religion?

☐ Christian ☐ Muslim ☐Hindu ☐Others

Reproductive characteristics

7. What is the patient's parity?.....*(Tick one)*

☐Nulliparous (none) ☐Primiparous (one) ☐Multiparous (2-4) ☐Grand multiparous (more than 5)

8. Have the patient ever been screened for cervical cancer in the past? (Pap smear or VIA/VILI or HPV-DNA testing)

☐Yes ☐No

9. At what age was the diagnosis of cervical cancer made? ……..

10. What symptoms did the patient first present with?

☐Per vaginal bleeding ☐per vaginal discharge ☐dyspareunia ☐ pelvic pain

HIV status

11. What is the patient's HIV status?

 Positive Negative

12. How long ago was the diagnosis made? ..... Years

13. Treatment with ARVs

 Yes No If yes, for how many years? …….

14. What is the patient's CD4 count?……. Viral load?

……

Pathological characteristics

15. FIGO stage at diagnosis *(tick one)*

☐ IA1 ☐ IA2 ☐ IB1 ☐ IB2 ☐IB3 ☐IIA1 ☐IIA2 ☐IIB

16. Histopathology (tick one)

Squamous Adenocarcinoma Adenosquamous Others (specify)……

17. Grading

1 2 ☐3

18. Lymph node involvement

☐Present ☐Absent

19. Lymphovascular space involvement

☐Present ☐Absent

20. Treatment modalities

☐Chemotherapy (cycles)…….

☐Radiotherapy (cycles)…….

☐Surgery (specify)……

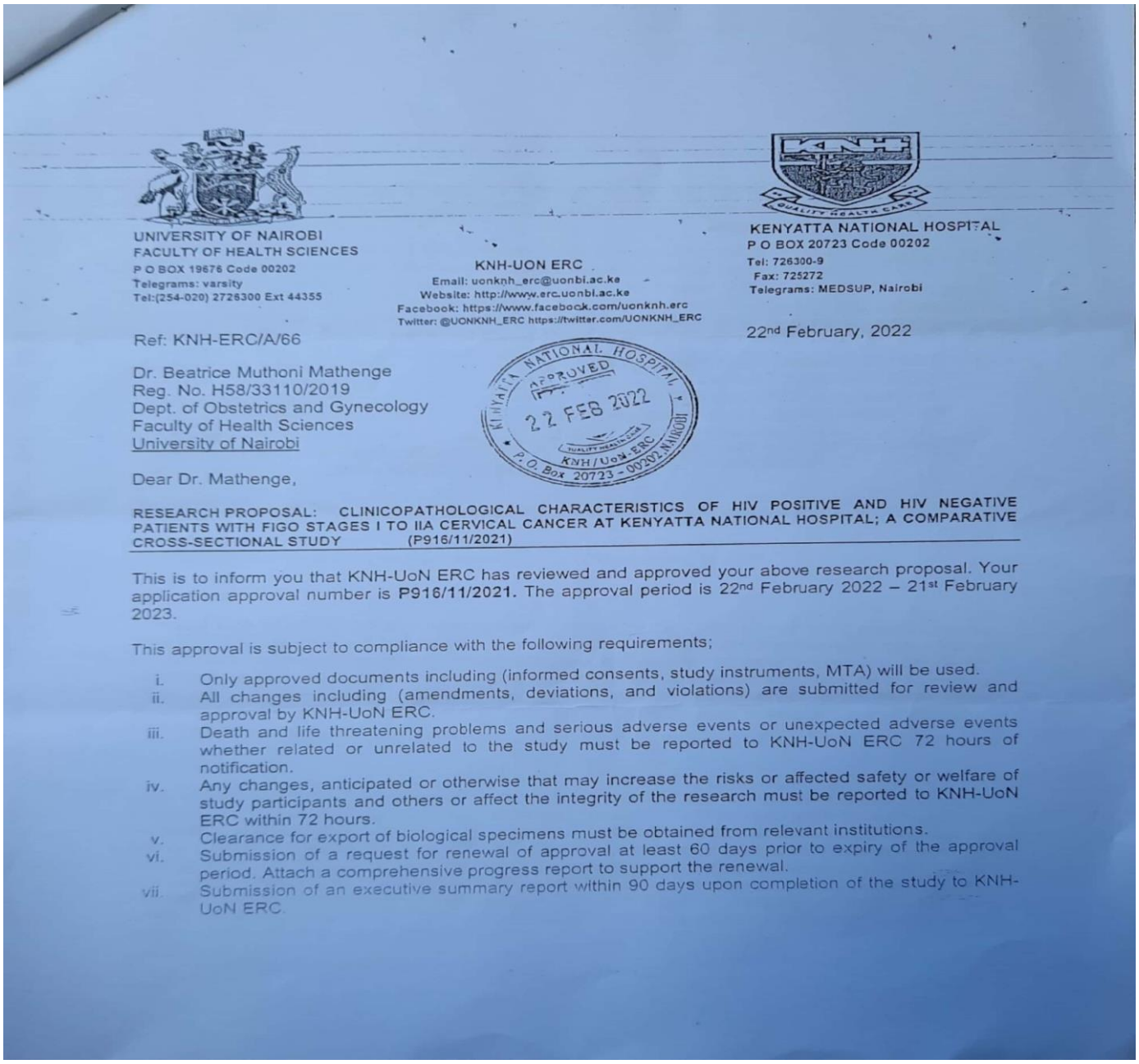
Combined treatment

21. Any other information

……

Thank you (End)

Appendix 2. KNH/UoN Ethics approval



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Ref: KNH-ERC/A/66

22nd February, 2022

KENYATTA NATIONAL HOSPITAL APPROVED 22 FEB 2022 KNH/UoN-ERC P.O. Box 20723 - 00202 NAIROBI

Dr. Beatrice Muthoni Mathenge
Reg. No. H58/33110/2019
Dept. of Obstetrics and Gynecology
Faculty of Health Sciences
University of Nairobi

Dear Dr. Mathenge,

RESEARCH PROPOSAL: CLINICOPATHOLOGICAL CHARACTERISTICS OF HIV POSITIVE AND HIV NEGATIVE PATIENTS WITH FIGO STAGES I TO IIA CERVICAL CANCER AT KENYATTA NATIONAL HOSPITAL; A COMPARATIVE CROSS-SECTIONAL STUDY (P916/11/2021)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P916/11/2021.** The approval period is 22nd February 2022 – 21st February 2023.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely,

DR. BEATRICE K.M. AMUGUNE
SECRETARY, KNH-UoN ERC

c.c. The Dean, Faculty of Health Sciences, UoN
The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Chair, Dept. of Obstetrics and Gynecology, UoN
Supervisors: Prof. Eunice Cheserem, Dept. of Obstetrics and Gynecology, UoN
Dr. Alfred Mokomba, Consultant Obstetrician and Gynecologist, KNH

Appendix 3. KNH approval

KENYATTA NATIONAL HOSPITAL
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OFFICE OF HEAD OF DEPARTMENT, OBSTETRICS & GYNAECOLOGY
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KNH/HOD-OBS&GYN/07/VOL.11/ Date: 25th February, 2022

Mathenge Beatrice Muthoni
Reg. No. H58/33110/2019
Dept. of Obstetrics & Gynaecology
Faculty of health science
University of Nairobi.

Dear Dr.Mathenge

RE: RESEARCH PROPOSAL – CLINICOPATHOLOGICAL CHARACTERISTICS OFHIV POSITIVE ABD HIV NEGATIVE PATIENT WITH FIGO STAGE I TO IIA CERVICAL CANCER AT KENYATTA NATIONAL HOSPITAL ;A COMPARATIVE CROSS SECTION STUDY [P916/11/2021]

This is to inform you that the department has given you permission to conduct the above study which has been approved by ERC.

Liaise with I/c Clinic 18 and HOD Health Information to facilitate your study.

You will be expected to disseminate your results to the department upon completion of your study.

Dr. Maureen Owiti
HOD-OBSTETRICS & GYNAECOLOGY

Cc.
- HOD-Health Information
- I/c Clinic 18

28 FEB 2022