RISK FACTORS FOR INVASIVE CERVICAL CANCER AMONG WOMEN LIVING WITH HIV/AIDS AT JARAMOGI OGINGA ODINGA TEACHING &REFERRAL HOSPITAL IN KISUMU COUNTY:A 5-YEAR HOSPITAL BASED CASE-CONTROL STUDY.

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DEDICATION

I dedicate this work, first and foremost to all HIV infected women. Most of all to one particular who inspired me to pursue this work, C.W aged 26years old diagnosed with cervical cancer postpartum at a young age and a mother of two but later on passed away. I also dedicate this work to all people with a passion for cervical cancer screening, as well as to all partners including the County Government of Kisumu.

LIST OF ABBREVIATIONS AND ACRONYMS

AIDS	-	Acquired Immunity Deficiency Syndrome
CCC	-	Comprehensive Care Clinic
HIV	-	Human Immunodeficiency Virus
HPV	-	Human Papilloma Virus
JOOTRH	-	JaramogiOgingaOdinga Teaching& Referral Hospital
W.H.O	-	World Health Organization

DEFINITIONS

The terms used are defined as follows:

1. **Cervical cancer screening**: the procedure of identifying and eliminatingatypical tissue in the cervix before cancer of the cervix develops. Screening methods for cancer of the cervix are the Pap smear test (conventional cytology), liquid-based cytology, the HPV DNA testing and the visual inspection with acetic acid or Lugol's iodine (VIA,VILI).
2. **Risk factors**: Those relatedto cancer of the cervix screening include socio-demographic, reproductive, medical and HIV related risk factors.
3. **HIV-infected woman**-any woman diagnosed with HIV and has been receiving care for HIV at JOOTRH between 2012-2016.
4. **Invasive cervical cancer** –a breach in the basement membrane occurs.This may advance to surrounding structures for example uterus,bladder,rectum and lymph nodes.
5. **Pap smear**: Known as Papanicolaousmear.It identifies primary cervical malignant cells situated at the transformation zone of the cervix.
6. **HIV-related care**- the care given at Comprehensive Care Clinic ranging from counselling,treatment of opportunistic infections,monitoring of CD4 count,screening for malignancies and checking adherence to ART .

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ABSTRACT

Background: According to WHO, almost nine out of ten (87%) cervical cancer deaths occur in the less developed regions. There were an estimated 311,000 deaths from cervical cancer worldwide in 2018, accounting for 7.5% of all female cancer deaths. Despite cervical cancer is the leading cause of cancer deaths among women in Kenya, the uptake of cervical cancer screening services remains low. HIV infection predisposes these women to persistent Human Papilloma Virus infection, the cause of invasive cervical cancer, which is an AIDS-defining illness. Kisumu County is heavily burdened by both of these infections but the utilization of cervical cancer screening services in the general population is low at 3%.Therefore there is a need for increased uptake of cervical cancer screening services among the HIV-infected women. This study seeks to establish the risk factors associated with invasive cervical cancer in this population, the socio-demographic, reproductive,medical and HIV-related risk factors

Broad Objective: It was to determine the risk factorsforcervical cancer among the HIV infected women with versus those without cervical cancer who received care at JOOTRH between 2012-2016.

Methodology: This was a 5-year unmatched case-control study with cases being HIV infected women with cervical cancer while controls were HIV infected women without cervical cancer. The study was conducted at JOOTRH in Kisumu County, Western part of Kenya.The study population involved HIV infected women with and without cervical cancer attending HIV and Gynecological clinic.

Sample size: File records of 100 cases and 100 controls were used for the study.

Data management and analysis: Data was collected by the use of structured questionnaires while data was analyzed using SPSS Version 21 and presented using tables. Bivariate analysis was carried out to compare the cases and controls, comparison between means was done using t-tests/ANOVA. Chi-squared tests wereused to compare propositions where results with $p<0.05$ was considered statistically significant. In multivariate analysis, the results were reported using Odds Ratios (OR) and 95% Confidence Intervals (CI), in results where confidence intervals for ORs did not include “1”, they were considered statistically significant.

Results:A total of200 files of HIV-infected women were reviewed.A higher proportion of women with a lower education level were found in cases than in the controls,58% vs 43%;p=0.028.Women with invasive cervical cancer had done more prior Pap smears compared to women without invasive cervical cancer,25%vs10%;p=0.008.Cases had a higher parity comparedto controls,4vs3;p=0.001.More controls had a CD4 count of more than 350 cells/mm3 compared to cases,83% vs 50%;p=<0.0001.In the multivariate analysis, compared to women who were coming from>4km away, controls were 5 times more likely to come from within 2km (OR=4.6,95%C.I is 1.62-12.9).Compared to controls, the cases were 5times more likely to have been screened (OR=4.6,95%CI is 1.3-16.3).Compared to women whose CD4 count was <200 cells/mm3, controls were 19 times more healthy with a CD4 count>500(OR=18.6,95% C.I is 4.0-86.6).

Conclusion: Generally in both cases and control there was a low uptake of cervical cancer screening, the cases had a low CD4 Count and lived further away from the hospital facility. Therefore there is a need to strengthen and increase the frequency of cervical cancer screening services in the CCC and to prioritize early treatment of cervical lesions in HIV infected women with a low CD4 count.

CHAPTER ONE

1.1 INTRODUCTION

1.1.1 Background

Cervical cancer is a surmountable global burden and highly preventable disease with the highest cancer mortality in reproductive women particularly in Low Middle Income Countries (LMIC) and amongst HIV patients. Globally, an estimated 311,000 deaths and 570,000 new cases were reported in 2018, accounting for 7.5% of all female cancer deaths(1). Almost nine out of ten (87%) cervical cancer deaths occur in the less developed regions(1).In Kenya, cervical cancer is the leading cause of cancer related deaths among women of reproductive age(1,2). Cervical cancer and HIV/AIDS are both major public health concerns in Kisumu County.HIV prevalence in Kisumu is 3.4 times the national prevalence at 19.9% as per 2015 HIV estimates(3).

Cervical cancer is an AIDS-defining malignancy. Once one develops invasive cervical cancer, it means they have acquired AIDS. Cervical cancer is the most common AIDS related malignancy (4). HIV influences the risk for cervical cancer through multiple biologic pathways. HIV increases the incidence and persistence of infection with oncogenic human papillomavirus (HPV), the causative agent in cervical cancer. HIV-infected women have a higher incidence and prevalence of cervical dysplasia and invasive cancer, a younger age of onset, present with more advanced malignancies and have lower survival rates than HIV-negative women (4).

There is paucity of data on the risk factors of cervical cancer amongst HIV infected women in Kisumu County. The aim of this study was to determine the risk factors for invasive cervical cancer among HIV-infected women based in this county.

CHAPTER TWO

2.1 LITERATURE REVIEW

2.1.1 Introduction

Cervical cancernegatively affects the lives of women in their reproductive age group in all aspects. The Kenya national guidelines on cervical cancerscreening, 2012, has estimated that the average life years lost due to cervical cancer is 25.3years (4).

Cervical cancer is preventable(5). However,only 5% of women in developing countries undergo screening for cervical cancer compared to over 40% in developed countries.Some countries have shown a marked reduction in incidence and prevalence of cervical cancer,more than 70%. Therefore in Low Middle Income Countries—where screening rates are very low—the majority of women present at late stages with invasive and advanced disease. Moreover, in Kenya only 3.2% of women aged18-69 years have been screened (6). It is an AIDS related malignancy (4), fortunately ART therapy has prolonged the lives of women living with HIV/AIDS,thus carcinoma of the cervix becomesa life changing process for this group of women affecting their quality of life.InKenya, a study was conducted among HIV infected women attending Comprehensive care clinics ,forty-three percent of the women had abnormal cervical cytological results. The presence of abnormal cervical cytology in HIV infected women is also much higher compared to the general population (3.6%) (5).Cervical cancer is an important cause of morbidity and mortality in Kenya,great efforts have been made to integrate screening of cervical cancer in the least comprehensive care package.

Nevertheless, it is shown that approximately eighty percent of HIV infected patients in Kenya are notcognisant of their HIV status(5). Therefore most of the women do not gain from the use of

screening programs for cervical cancer at the Comprehensive Care Clinics. Thus this group of women pose a high risk of acquiring cervical cancer and necessitates frequent screening of cervical cancer compared to the general population (7). It is one thing to have the cervical cancer screening strategy in place in an HIV Comprehensive Care Centre (CCC) and another thing for those who are expected to benefit from it to utilize the service (5). Cancer of the cervix is thus a preventable disease.Screening at first contact then repeat screening after six months if negative, subsequently the woman should continue on an annual screening for life (8).

Primary preventive measures include healthy lifestyles and HPV vaccine while secondary prevention can be achieved through frequent screening and managementof lesions of the cervix by management options currently available in Kenya. For HIV positive women to avoid this killer disease, they have to screen for cervical cancer lesions frequently which is a secondary preventive measure. The Kenyan governmentvia the Reproductive Health Division has confirmedincorporation of this service into the repetitive care of women living with HIV/AIDS, in all Comprehensive Care Clinics and has moved a stage further in teaching health care workers on how to go about the `see and treat` approach.

2.1.2 Screening Practice of cancer of cervix among women living with HIV/AIDS.

WHO commendsaggressiveness in the screening of cervical cancer and management plan for HIV infected women than for HIV uninfected women. In cervical cancer agendas,females should also be screened for HIV. Thus taken together, cervical cancer prevention would compriseevidence, learning, communication, screening and management in a single visit approach(9).

In spite of the aforesaid WHO approvals and accessibleopportunities for integration in many low middle income countries, prevention of cancer of cervix and HIV infection to be implemented as separateagendas. For instance, in Nigeria, astudy was conducted among women living with HIV inattendanceof post-HIV test counselling designated that no patient was informed about cancer of the cervix and its screening during post-test counseling sessions (7).Likewise, a study done in Uganda among healthcare workers and policy strategists confirmed that much occursconcerning the possibility of HIV and integration of screening for cancer of the cervix., nearlyall of HIV care plans in Uganda do not give services for cervical cancer patients, therefore, women attending HIV clinics miss screening opportunities despite the frequent visits they make to HIV clinics. A lesser amount ofscreening for cervical cancer, its destructivenature progresses in HIV infected women leading to advanced carcinoma withmeagre prognosis(10).

In Kenya, cervical cancer screening services have been integrated into the MCH-FP clinic for well-baby and mother. A large number ofwomen benefitted from this service through one of the future gains from this study is to seek incorporation of HIV clinics with screening for cervical cancer so as to offer bidirectional service. In a study done in Nigeria showed bidirectional service was offered in both Reproductive Health and HIV care clinics (10).

There still exists a gap between the screening practices of these women and the development of cervical cancer considering the uptake of screening is still low generally. Possibly a comparison in the risk factors between those with cervical cancer and those without would give plausible explanations as to the existence of the gap in this group.

2.1.3Characteristics contributing to cancer of the cervix among women living with HIV/AIDS

HIV and cancer of the cervix are interconnectingdiseases that both inexplicably affect women of resource constrained regions. The effect ofinequality and biologic interaction of these two diseases is understoodintensely inKenya. Women living with HIV/AIDSare at greater risk for the proliferation of pre-cancer cervical lesions.They grow more aggressive lesions due to higher levels of immunosuppression and are affected at an earlier age.A research done in Nigeria among HIV infected women in 2013 at Abuja in two medical institutions showed that HIV infected women are at a slightlygreater threat for cervical pre-cancer and cancer. The research highlighted the significance of screening women for cancer of the cervix especially those living with HIV in Nigeria(11). Infection with HIV and areduced CD4 Count are related with an increase in sexual behavior. According to a prospective multicohort study done in North America, in 2013 demonstrated women living with HIV and astandard CD4 count of more than 350 cells/mm^3 a double in incidence of cancer of the cervix. (12).

In Ethiopia, at Jimma University Hospital in 2010 on risk factors associated with invasive cervical cancer,anunnmatched case-control research was done.Older women more than forty years,more than one husband, as well as more than one wife in lifetime, women who had more

than 4 children, and more than 25years of age at first delivery, were considered important statistically and the last two were individuallyrelated to cancer of the cervix.

2.1.4The National Cancer Screening Strategy

This plan targets women between twenty-five to forty years of age, though women of other age groups who are willing to screen are offered the service. All women living with HIV, an onset of sexual debut, more than eighteen years old are screened for cancer of the cervixincorporated in the HIV comprehensive care. The screening sequence of HIV infected women as compared to those who are uninfected (once in every 5 years if with normal results) is as follows; at diagnosis, after six months in the first year, and then annually if normal (5).

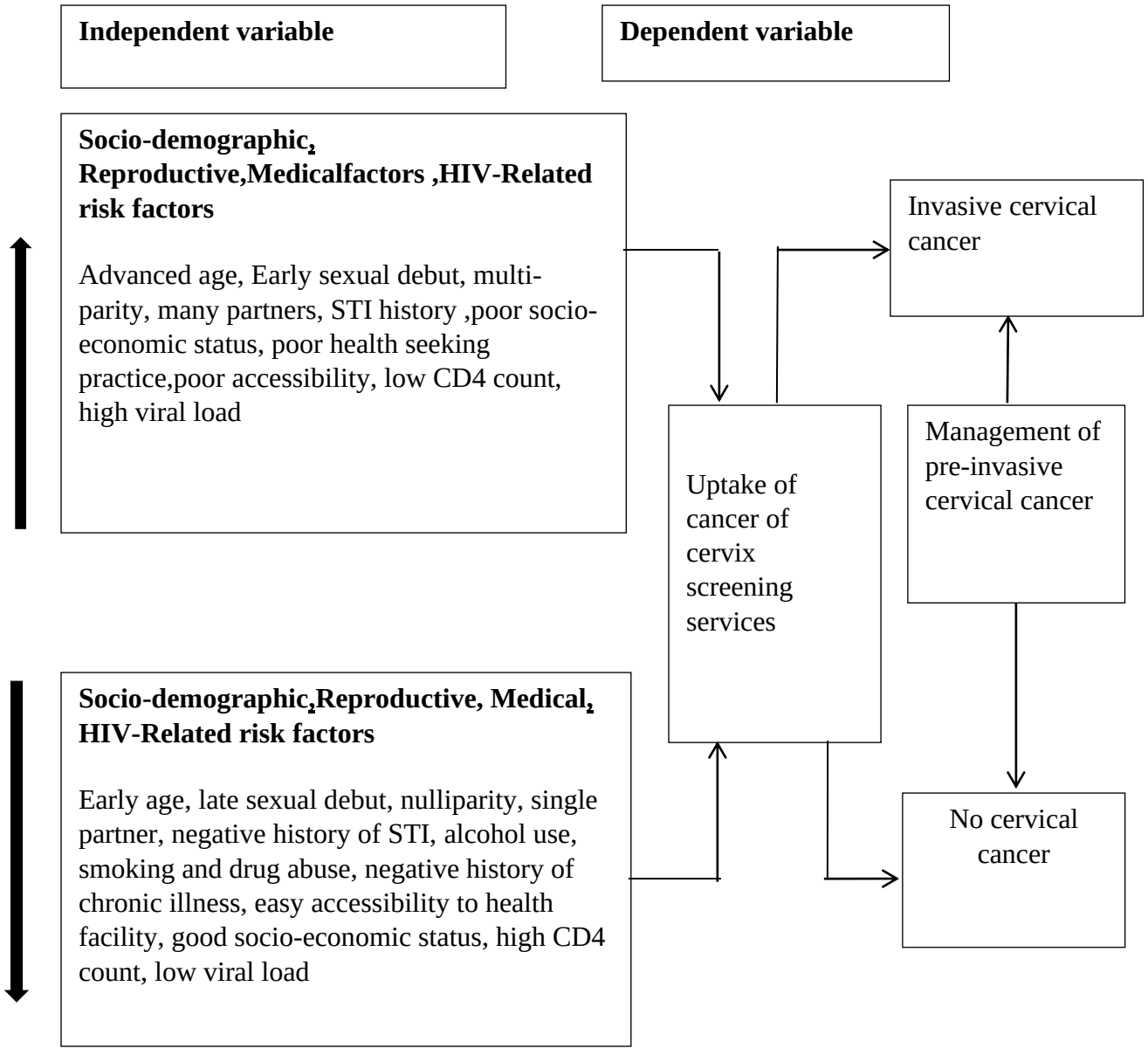
2.2 JUSTIFICATION

The utilization of cancer of the cervix screening services among HIV infected women in JOOTRH in Kisumu County is crucial since cervical cancer and HIV are both transmitted sexually and among those with cancer of the cervix, it is an AIDS-defining illness. Women living with HIV are likely to present with cervical cancer in their lifetime therefore prevention of cervical cancer is necessary among these women especially as more women are living longer with HIV.Screening these high-risk patients allows cervical cancer to be diagnosed in advance thus providing the best opportunity for primary prevention and treatment.

Further understanding of the risk factors of invasive cervical cancer among this population may guide prevention and treatment.

2.3 CONCEPTUAL FRAMEWORK

In the conceptual framework, the independent variable represents both the positive and negative risk factors of invasive cervical cancer while the dependent variable represents uptake of cervical cancer screening services and whether or not one has invasive cervical cancer and if one has sought treatment for pre-invasive cervical cancer. Risk factors such as advanced age, early age at sexual debut, multiparity, multiple partners, positive history of STIs, poor socioeconomic status, poor health seeking practice, long distance to health facility, low CD4 count and high viral load have a low uptake of cervical cancer screening therefore are at high risk of acquiring invasive cervical cancer and less women tend to seek treatment of pre-invasive cancer lesions before it progresses to invasive cervical cancer. While the opposite of the aforementioned risk factors have an increased uptake of cervical cancer screening and more women and tend to seek treatment of pre-invasive cancer lesions. Figure 1 below shows the conceptual framework:



2.4 RESEARCH QUESTION

What are the risk factors forinvasive cervical cancer among HIV infected women who received HIV-related care at JaramogiOgingaOdinga Teaching and Referral Hospital between 2012-2016?

2.5HYPOTHESIS

Null Hypothesis

There are no risk factors for invasive cervical cancer among HIV infected women

2.6 STUDY OBJECTIVES

2.6.1Broad Objective

To determine the risk factors for invasive cervical cancer among HIV infected women who received HIV-related care at JOOTRH between 2012-2016.

2.6.2 Specific Objectives

Among HIV-infected women who received HIV-related care at JOOTRH between 2012-2016:

1. To comparethe cervical cancer screeningpracticesbetween those with and without invasive cervical cancer.
2. To compare the reproductive risk factors between those with and without invasive cervical cancer.
3. To comparethe HIVrelated factors and medical characteristics between those with and without invasive cervical cancer.

CHAPTER THREE

3.1 METHODOLOGY

3.1.1 Study Design

This was an unmatched 5-year case-control study between 2012-2016 in which records of 100 cases of HIV infected women with a histological diagnosis of invasive cervical cancerwere reviewed and compared with records of 100controls of HIV infected women without a histological diagnosis of invasive cervical cancer in order to determine the factors associated with the risk of invasive cervical cancer.

3.1.2 Study Setting

This study was conducted at JOOTRH inKisumu which is the largest referral hospital in Western Kenya. It also has the biggest support centre for HIV infected patients in the region and a lot of research based studies are conducted in this facility especially concerning HIV/AIDs. It has a good network communication with other peripheral facilities,researchcentres and external programmes from other regions.

Cervical cancer screening is mainly done at the Comprehensive Care Clinic (CCC) since 2015. The CCC reviews an average of 3600-4000 patients monthly with a good coverage of staff workers ranging from obstetricians to nurses. Amongst women, an average of 70-120 patients are screened monthly. The Gynecological clinic where oncology patients with invasive cancer are seen upon diagnosis of their HIV status, are then linked to the CCC. Patients with invasive cervical cancer are confirmed through EUA/ Staging and biopsy. The histopathology is conducted in an ISO certified private facility with a pathologist in close proximity to JOOTRH. Other cancer screening methods used in the gynecological clinic and CCC included VIA/ VILLI and Pap Smear performed by the attending nurses and reviewed by the clinicians with abnormal

findings. These screening tests are done annually. There are no colposcopic services offered in JOOTRH. All HIV patients are counselled, partners testing offered; put on antiretroviral therapy and followed up for with biomarker of CD4 and viral load; adherence to therapy and psychosocial support is also given.

3.1.3 Study Population

This comprised of the cases who were HIV infected women with a histological diagnosis of invasive cervical cancer while controls were HIV infected women without a histological diagnosis of invasive cervical cancer attending Comprehensive Care Clinic and Gynecological clinic at JOOTRH in Kisumu County.

3.1.3.1 Inclusion Criteria

1. HIV positive women who attended JOOTRH from 2012-2016, within Kisumu.
2. Women from the reproductive age group 18+

3.1.3.2 Exclusion Criteria

1. Patients without HIV serology.
2. Patients without invasive cervical cancer and a histopathological report of cervical biopsies taken.

3.1.4 Study Procedure

3.1.4.1 Selection of cases and controls

Permission to collect data was sought from the head of department of human resource in CCC and gynecological clinic. Data was collected randomly from records of patients' files from 2012-2016 and entered into a structured questionnaire. Files were collected from CCC of all HIV infected women, starting from 2016 ,the records for controls were selected for patients who received care at the same time with every case that received care for invasive cervical cancer. More files were picked from gynecological clinic for cases and those files selected were ensured

to have had linkage from CCC from 2012-2016. Therefore convenient sampling of 100 cases and controls wasundertaken in both the CCC and gynecology clinic. The files for cases were ensured to have a histological diagnosis of invasive cervical cancer from an ISO certified centre while controls were without the diagnosis. All data was entered into a structured questionnaire and safely stored for data analysis.

Study flow chart

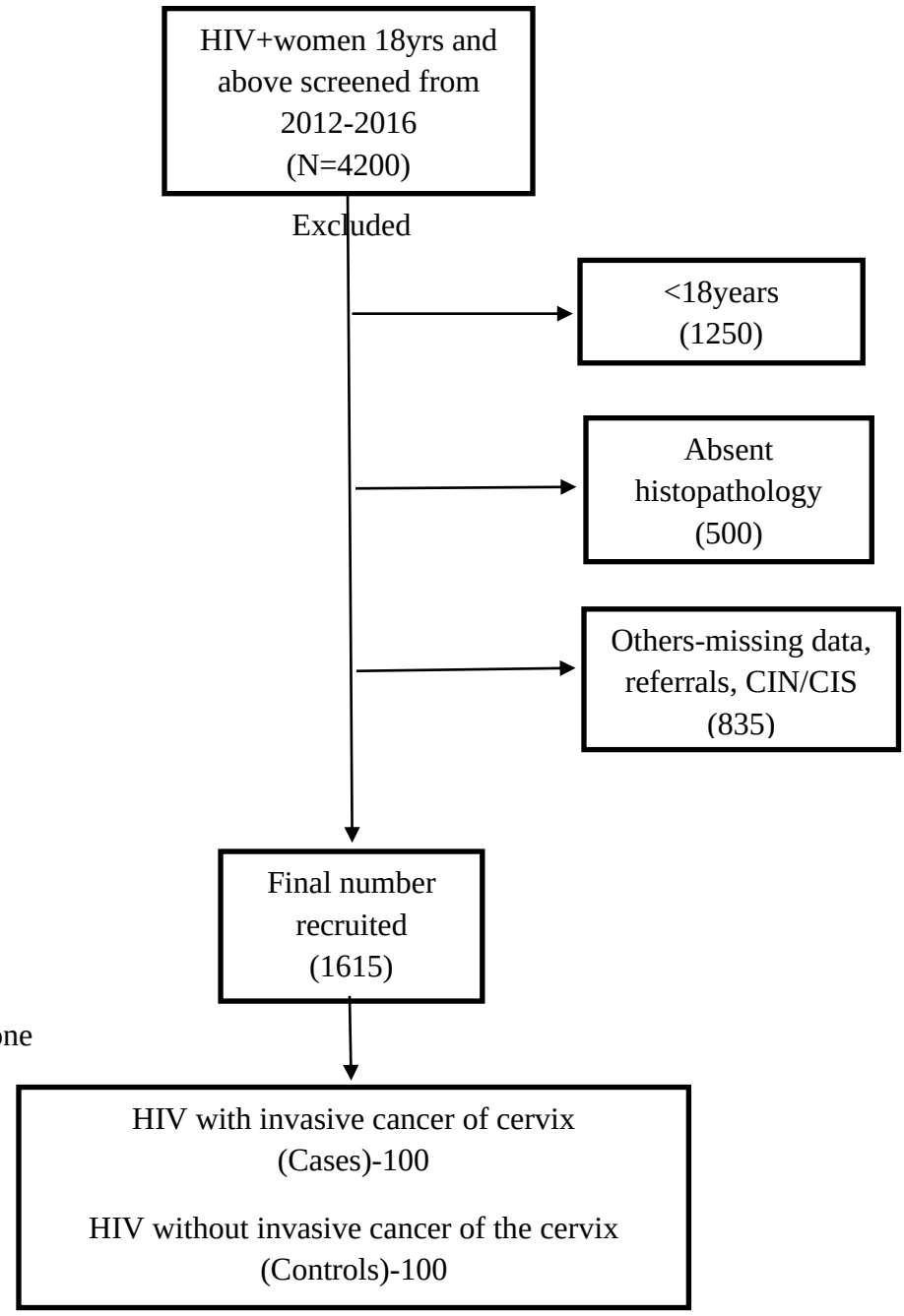


Figure 1: Study flow chart showing recruitment of records of participants in the study

3.1.5 Sample Size

$$n = (\frac{r+1}{r}) \frac{(\bar{p})(1-\bar{p})(Z_{\beta} + Z_{\alpha/2})^2}{(p_1 - p_2)^2}$$

Fleiss, Statistical Methods for Rates and Proportions, formulas 3.18 &3.19(13).

Where;

p_1 = proportion of controls with exposure (here 15% of cancer-free women exposed to screening)

p_2 = Hypothetical proportion of cases with exposure (here 3% of cancer-free women exposed to screening)

r = ratio of controls to cases (here the equal ratio of cases to controls r=1)

Z_{β} = Represented the desired power (typically .84 for 80% power)

Z_{α} = Represented the desired level of statistical significance (typically 1.96 for 95% confidence).

n = Sample size in the case group (here n=90 ➔90 women with invasive cervical cancer and 90 without)

n = **Sample size** in the case group

$$n = (\frac{1+1}{1}) \frac{0.09(1-0.09)(1.96+0.84)^2}{(0.15-0.03)^2}$$

n=90 ➔90 women with invasive cervical cancer and 90 without)

3.1.6 Data Management and Analysis

Data werecollected using structured questionnaires and entered into a password-protected Microsoft Access Database. The hard copy data forms were stored in a lockable cabinet in the Principal Investigator's office during collection and after analysis. These were moved to a lockable cabinet in the statistician's office during data entry and analysis. Upon completion of Data entry, hard copy forms were compared with the entered data to identify errors and corrections made appropriately.100 files each with cancer positive and cancer negative were randomly selected from 2012 to 2016 and data extracted, and then filled into questionnaires.

Descriptive statistics werecarried out where discrete variables were summarized with frequencies and percentages while continuous variables were summarized using measures of central tendency and dispersion such as mean, median, mode, standard deviation, and inter-quartile ranges.

Bivariate analysis was performed to compare the cases and controls in terms of socio-demographic characteristics, reproductive history, other co-morbidities, and cervical cancer screening history. Comparison between means was done using t-tests/ANOVA while chi-squared tests wereused to compare propositions where results with $p<0.05$ was considered statistically significant. In multivariate analysis,the association between cancer screening and the development of invasive cancer was determined while adjusting for confounders and effect modifiers. This was achieved using binary stepwise backward logistic regression. These results were reported using Odds Ratios (OR) and 95% Confidence Intervals (CI). In results where confidence intervals for ORs do not include "1", these were considered statistically significant.

All analysis was carried out using IBM Statistics Software Version 21 and presented using tables.

Data collection tool was summarized in Appendix I

Tables with data variables were summarized in Appendix II

3.2 ETHICAL CONSIDERATIONS

Approval to conduct this study was obtained from the Kenyatta National Hospital / University of Nairobi Ethical Review Committee (P738/12/2017) as well as JaramogiOgingaOdinga Teaching and Referral Hospital Ethics Board (ERC/IB/VOL.I/444).Ethical issues related to this study included preservation of privacy and confidentiality ofpatient's record files while retrieving data. It was the duty of the physician involved in research to protect the life, health, dignity, integrity, right to self-determination of personal information on retrieval of data from patients' records. Also, to avoid falsification of data, thus to uphold honesty and integrity. And after publishing the results, to employ beneficence to the hospital and community by presenting to them the results.

3.3 STUDY LIMITATIONS

1. Retrieval of old files-encountered difficulties retrieving older files e.g. 2012 files

   This was minimized by collecting files from the most recent years i.e. 2016 and finalizing with 2012 files which may be more difficult to retrieve.
2. Missing data-some essential data was missing from the documentation in some files.Any file that was missing more than 50% of the required data was discarded e.g viral load
3. Selection bias-this was minimized by random sampling of 100 cases and controls of cancer positive and negative among the HIV infected from 2012 -2016

3.4 STUDY STRENGTHS

1. This was a pioneer study among HIV infected women in Kisumu County.

2. The study involved a rare outcome therefore a case control study was ideal.
3. It was safe and affordable to conduct the study.

CHAPTER FOUR

4.1 RESULTS

SOCIO-DEMOGRAPHIC FACTORS

A total of 100 patient records were studied for cases and 100 for controls. Socio-demographic factors are shown below in Table 1.Cases were less likely to have attained secondary level education and more, less likely to have a source of income and permanent homestead, covered longer distances (>4km) to the health facility and were more likely to use public means of transport than controls. These differences were statistically significant (p value <0.05), as shown in Table 1.

Table 1: Socio-demographic characteristics among cases and controls.

Characteristic	Cases N=100 n (%)	Controls N=100 n (%)	OR[95%C.I]	p-value
Age(years)				
<30	2(2)	2(2)	1.0[0.02-	0.944
30-34	8(8)	5(5)	50.40]	
35-40	22(22)	22(22)	0.6[0.03-	
>40	68(68)	71(71)	12.41]	
Education			1.0[0.06-	
<Secondary ≥Secondary	57(58)41(42)	43(43)	17.02]	**0.028**
Marital status		57(57)	1.0[0.06-	
Single	2(2)62(71)-24(27)	7(7)66(70)-	17.03]	
Monogamous Polygamous		23(24)		0.271
Divorced/Separated			1.84	
Employment status	75(76)14(14)10(10)-		[1.05-3.24]	
Self-employed Salaried		73(75)24(25)0(0)		
Housewife Student		-	Ref	
Type of homestead	64(67)31(33)		0.30[0.06-	**0.002**
Semi-permanent Permanent			1.52]	
Distance to facility		50(51)49(50)	-	
Less than 1km1-2km2-	-		0.27[0.05-	
4km>4km	1(1) 25(25)		1.46]	
Means of transport	73(74)	-		
BicycleMotorbikeMatatuPrivate		3(3) 61(61)		**0.015**
car		36(36)	Ref	
	-		1.76[0.85-	
	3(3)95(97)		3.67]	
	-	-	-	**<0.0001**
		12(12)88(88)	-	
		-		
			2.02[1.13-	
			3.62]	
				0.017
			-	
			Ref	
			0.81[0.08-	
			8.20]	
			0.16[0.02-	
			1.64]	
			-	
			Ref	
			0.23[0.06-	
			0.85]	
			-	

Women with invasive cervical cancer were more likely to have donepap smears compared to women without invasive cervical cancer (25% vs 10%, p=0.008), had a higher parity (4 vs 3, p = 0.001), and had a low uptake of family planning use (40% vs 79%, p=<0.0001) as shown in table 2.

Table 2: Reproductive health factors among cases and controls.

Factor	**Cases n (%)**	**N=100**	**Controls n (%)**	**N=100**	**OR[95%C.I]**	**p-value**
Pap smear test						
Yes	24(25)	72(75)	10(10)	87(90)	2.9[1.30-6.46]	**0.008**
No						
Parity No.	4		3	3		
of live births No. of	4	1	0		Ref	**0.001**
miscarriages					1[0.12-8.31]	**<0.0001**0.53
No. of sexual partners	91(99)	1(1)	95(99)	1(1)	-	
1-2	-		-			1.0
3-4					Ref	
>4					1[0.06-15.54]	
Current partner circumcised	3(38)5(63)		25(48)	27(52)	-	
Yes No	18(100)0(0)		8(89)39(49)			0.58
STIs					0.65[0.14-3.0]	
Yes						
No	40(40)		79(79)			0.150
Types of family planning	60(60)		21(21)		-	
Yes						
No						**<0.0001**
					5.6[3.02-10.55]	

As shown in table 3, HIV-related factors significantly associated with risk of invasive cervical cancer were shorter duration of HIV infection and last CD4 count while women without invasive cancer had a higher proportion of discordant couples.

Table 3:HIV related factors among cases and controls

Factor	Cases N=100 n (%)			Controls N=100 n (%)			OR[95%C.I]	p-value
Duration of HIV infection <5years								
5-10 years >10 years	22(24)	57(61)	14(15)	1(1)	75(76)	23(23)	Ref 29[3.8-221.1] 36[4.4-298.5]	ref**0.0010.001**
Opportunistic infections	75(81)		18(19)	73(75)		24(25)		0.371
Yes								
No	14(39)		4(11)	5(5)			1.37[0.69-2.73]	
Last CD4 count	14(39)		4(11)	12(12)		49(50)		ref
<200 200-350 350-500>500				33(33)			Ref 8.4[1.83-38.5] 9.8[3.01-31.9] 23[5.39-99.1]	**<0.0001<0.0001** 0.048 **0.017**
Discordant couples				8(9)		82(91)		
Yes No	98(100)		-					
Use of ART therapy				99(100)		-		
Yes No	97(98)		2(2)				0.12[0.01-0.95]	-
Adherence to ART				100(100)		0(0)		
Yes							-	
No								0.153
							-	

Key: ART-Anti-retroviral therapyCD4-Cluster of Differentiation 4

In medical factors, findings were similar in both cases and controls. There was no statistical significance found as shown in Table 4 below:

Table 4:Medical characteristicsamong cases and controls

Characteristic	Cases N=100 n(%)	Controls N=100 n(%)	OR[95%C.I]	P-value

Alcohol							
Yes		1(1)97(99)		0(0)	100(100)	-	0.314
No							
Smoking		-		-			
Yes		98(100)		98(100)		-	
No							-
Substance abuse		(-)		(-)			
Yes	No	100(100)		100(100)		-	-
Diabetes							
Yes	No	1(50) 1(50)		6(86)			
Hypertension				1(14)		0.17[0.01-5.45]	0.284
Yes	No	1(50)	1(50)				
Asthma				5(71)			
Yes	No	0(0)2(100)		2(30)		0.4[0.02-10.01]	0.57
				1(14)6(86)			
						-	0.57

LOGISTIC REGRESSION

The variables that showed statistical significance after the multivariate analysis was performed and are as shown in table 5 below. The distance from the facility was an approximate estimation of patients'location from the health facility(JOOTRH).

Table 5: Logistic regression among cases and controls

Factor		Odds Ratio (95%C.I)	P-value	
Distance from facility				
>4km		ref 2.5(0.14-	**0.016**0.537	
2-4km		41.84)4.6(1.62-12.90)	**0.004**	
<2km				
		4.6(1.28-16.30)	**0.019**	
Pap smear				
CD4 Count		ref 12.8(2.40-68.54)	**0.001**	
<200	200-350	12.6(3.36-47.30)	**0.003**	0
350-500	>500	18.6(4.01-86.2)	0	

In terms of distance from the facility, compared to women who are coming from more than 4km away, the controls were 5 times more likely to come from within 2km (OR 4.6,95%C.I 1.62-12.9).While in the screening profile,compared to controls,women who were living with invasive cervical cancer were 5 times more likely to have been screened(OR 4.6,95%C.I 1.3-16.3).In the CD4 count,it was found that compared to women whose CD4 count was less than 200 cells/mm3,controls were 19 times more healthy with a CD4 count of more than 500 cells/mm3(OR 18.6,95%C.I 4.0-86.6)

CHAPTER FIVE

5.1 DISCUSSION AND CONCLUSION

The findings of this study revealed that HIV infected women with invasive cervical cancer are more likely to live far from hospital, have no salaried income, have lower education levels, live in semi-permanent homesteads, were housewives and used public means of transport. This group

were also noted to have lower CD 4 Counts, increased screening, high parity >4 and live births and having HIV infection for shorter duration as compared to those without invasive cervical cancer.

In the sociodemographic factors, the mean age for cases was 47 years while controls was 46 years, as compared to a study done in Nigeria by Ononogbu et al, the median age was 32 years(12), and median age in a recent study done among HIV-positive women in Dagoretti county in Kenya by Lukorito et al was 33 years,(5).More women had below secondary school education level in cases than in controls,58% vs 43%,p=0.028, this is similar to a study done by Wanyenze et al in Uganda,(14).There were more women with a source of income in controls than in cases,100% vs 90%,p=0.002,whereby most were self-employed with their own businesses. This is similar to the study done in Dagoretti county in Kenya that showed a bigger proportion of the respondents were salaried employees,50%,(5).Women with invasive cervical cancer were less likely to have a permanent homestead compared to women without invasive cervical cancer,33% vs 50%,p=0.015.Women with invasive cervical cancer were coming from further away from the health facility(>4km) compared to those without invasive cervical cancer,74% vs 36%,p=<0.0001.Therefore they were more likely to use matatus to reach the health facility than their counterparts,97% vs 88%,p=0.017.Unlike a study was done by Wanyenze in Uganda that showed cervical cancer screening services was independent to the distance to a health facility, no variation was observed (14).Cases who had increased distances to the health facility plausibly affected their access and health seeking behavior giving them late presentation with invasive cervical cancer. Generally women with poverty and lower education levels have increased vulnerability to having invasive cervical cancer due to lack of awareness and information.

In terms of the cervical cancer screening, women with invasive cervical cancer had done more prior pap smears compared to women without invasive cervical cancer,25% vs 10%,p=0.008.Compared to other recent studies done by Lukorito in Kenya and Wanyenze in Uganda, the general uptake of cervical cancer screening was low,(5)(14),and in contradiction to a study done by Adjorlolo in Cote d'Ivoire among HIV infected women as cases while controls were HIV negative women, it showed that controls had done more prior Pap smears compared to cases,16% vs 7%,p=0.004,(15). Possible reasons for these findings could have been amongst those screened with Pap smear, denial of report findings or repetitive reaffirmation can account for the increased screening done on the cases compared to controls. Additionally, it is expected that those who live far from hospital would not be able to seek screening services or have their ARV drugs refilled, interestingly the ones with invasive cancer were more likely to have done a pap smear. This was unusual since a pap smear is a screening tool, it is possible that the pap was done as a result of symptomatology and therefore diagnosed the cancer.

In the reproductive factors and sexual behaviour, the cases were found to have a higher parity compared to controls 4 vs 3, p=0.001,similar to study done by Wanyenze(14). High parity and live births increase the risk for HPV oncogenic sub types.While in HIV-related factors, in terms of HIV staging among these women, compared to stage I,stage II and IV had more cases than in controls, this was similar to the study done by Adjorlolo in Cote d'Ivoire(15).76% of controls had lived with HIV for more than 5 years compared to cases(61%) within the same duration. p=0.001.Women who lived with HIV for more than 10 years, there was a higher proportion among controls compared to cases,23% vs 15%,p=0.001.More controls had a CD4 count of more than 350 cells/mm3 compared to cases,83% vs 50%,p=0.0001,this was in agreement with a study done by Ononogbu et al in Nigeria (12) that showed that both HIV positive and negative women

with higher CD 4 count had a lower incidence of cervical pre-cancerous lesions. Invasive cervical cancer is an AIDS defining illness(4) and thus the lower CD4 counts and the more aggressive spread of cervical cancer is found amongst the cases, while in those with a HIV duration for over 5 and 10 years in the controls it may be possibly protective due to ART therapy and follow up in CCC. In the discordant couples 1: 9 had invasive cervical cancer which implies protection of the controls in this study

CONCLUSIONGenerally in both cases and control there was a low uptake of cervical cancer screening, the cases had a low CD4 Count and lived further away from the hospital facility. Therefore there is a need to strengthen and increase the frequency of cervical cancer screening services in the CCC and to prioritize early treatment of cervical lesions in HIV infected women with low CD4 count.

5.2 RECOMMENDATIONS

There is need to have policies that provide:

1. Equitable access,coverage and frequent cervical cancer screening services.
2. Gender empowerment for HIV infected women.
3. Early treatment of cervical lesions in HIV infected women with lowCD4 count.

6.0 TIMELINES

Time / Activity	Dec 2017	Jan to March 2018	April to May 2018	Sept to Nov 2018	Jan to May 2019	June 2019	July 2019

Proposal development							
Submission to KNH/UON_ERC and Approval							
Submission to Ethics at JOOTRH and approval by Ethics at JOOTRH							
Conducting research/preliminary results							
Data analysis and presentation of results to the Department of Obs&Gyn							
Submission of the thesis to theDepartment of Obs&Gyn							
Manuscript write-up & publication							

Figure 2: A Gantt chart showing timelines versus activities throughout the study period

7.0 BUDGET

Table 2: A table summarizing the budget

ITEM	**No.of items**	**Cost of item**	**TOTAL AMOUNT(KSH)**
Ethical review at JOOTRH	-	6050	6050

Use of a statistician	1	60000	60000
Use of a co-investigator	2	6000	12000
Transport	-	20000	20000
Use of stationery (paper, pen/pencils	-	10000	10000
Typing	-	5000	5000
TOTAL AMOUNT			**113,050**

8.0 REFERENCES

1. World Health Organization. Comprehensive cervical cancer prevention and control : a healthier future for girls and women. World Heal Organ [Internet]. 2013;1–12. Available from: www.who.int

2. Korir A, Okerosi N, Ronoh V, Mutuma G, Parkin M. Incidence of cancer in Nairobi ,

Kenya (2004 – 2008). 2015;2059:2053–9.

3. National AIDs Control Council. Kenya HIV County Profiles 2016 i [Internet]. 2016. Available from: http://nacc.or.ke/wp-content/uploads/2016/12/Kenya-HIV-County-Profiles-2016.pdf

4. Mungo C, Cohen CR, Maloba M, Bukusi EA, Huchko MJ. Prevalence, characteristics, and outcomes of HIV-positive women diagnosed with invasive cancer of the cervix in Kenya. Int J Gynaecol Obstet [Internet]. 2013;123(3):231–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24095308%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4151462

5. Lukorito J, Wanyoro A, Kimani H. Uptake of Cervical Cancer Screening among HIV Positive Women in Comrehensive Care Centres in Nairobi , Kenya. 2017;5(1):1–6.

6. Parkin DM, Bray F, Ferlay J, Pisani P. Global Cancer Statistics , 2002. 2002;

7. Dim CC, Nwagha UI, Ezegwui HU, Dim NR. The need to incorporate routine cervical cancer counselling and screening in the management of women at the outpatient clinics in Nigeria. J Obstet Gynaecol. 2009 Nov;29(8):754–6.

8. Mortality Weekly Report. Morbidity and Mortality Weekly Report Sexually Transmitted Diseases Treatment Guidelines , 2006 depar tment of health and human ser. Vol. 55. 2006.

9. Gichangi P, Estambale B, Bwayo J, Rogo K, Ojwang S, Opiyo A, et al. Knowledge and practice about cervical cancer and Pap smear testing among patients at Kenyatta National Hospital, Nairobi, Kenya. Int J Gynecol Cancer. 2003;13(6):827–33.

10. Kumakech E, Andersson S, Wabinga H, Berggren V. Integration of HIV and cervical

cancer screening perceptions and preferences of communities in Uganda. 2015;1–13.

11. Morema EN, Atieli HE, Onyango RO, Omondi JH, Ouma C. Determinants of Cervical screening services uptake among 18 – 49 year old women seeking services at the Jaramogi Oginga Odinga Teaching and Referral Hospital , Kisumu , Kenya. 2014;

12. Ononogbu U, Almujtaba M, Modibbo F, Lawal I, Offiong R, Olaniyan O, et al. Cervical cancer risk factors among HIV-infected Nigerian women. BMC Public Health [Internet]. 2013;13(1):1. Available from: BMC Public Health

13. Fleiss JL. Statistical Methods for Rates and Proportions. 1st Editio. John Wiley & Sons, London; 1981. 218 p.

14. Wanyenze RK, Bwanika JB, Beyeza-Kashesya J, Mugerwa S, Arinaitwe J, Matovu JKB, et al. Uptake and correlates of cervical cancer screening among HIV-infected women attending HIV care in Uganda. Glob Health Action [Internet]. 2017;10(1). Available from: https://doi.org/10.1080/16549716.2017.1380361

15. Adjorlolo-Johnson G, Unger E., Boni-Ouattara E, Touré-Coulibaly K, Maurice C, Vernon SD, et al. Assessing the relationship between HIV infection and cervical cancer in Côte d'Ivoire: A case-control study. BMC Infect Dis [Internet]. 2010;10. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L359494933%5Cnhttp://www.biomedcentral.com/1471-2334/10/242%5Cnhttp://dx.doi.org/10.1186/1471-2334-10-242%5Cnhttp://wt3cf4et2l.search.serialssolutions.com?sid=EMBASE&issn=14712334&id

9.0 APPENDICES

Appendix I: Data collection tool

PART 1: SOCIODEMOGRAPHIC FACTORS

PART 2: CERVICAL CANCER SCREENING

PART 3: SEXUAL AND REPRODUCTIVE FACTORS

PART 4: MEDICAL AND HIV-RELATED RISK FACTORS

The questionnaire below was used as a data collection tool to retrieve data from patients' files, both cases, and controls.

STUDY QUESTIONNAIRE

PART 1: SOCIO-DEMOGRAPHIC FACTORS

1. Study ID _____
2. Date (day/month/year) ___/___/_____
3. Age _____
4. Gender Male☐ Female ☐
5. Education Level

    ☐ Non-formal education

    ☐ Primary education

    ☐ Secondary education

    ☐ Tertiary education

6. Marital status

   ☐ Single

   ☐ Married (monogamy)

   ☐ Married (polygamy)

   ☐ Divorced/separated

7. Employment status

   ☐ Self-employed

   ☐ Salaried

   ☐ Housewife

   ☐ Student

8. Household Monthly Income

   ☐ Less than 5000

   ☐ Between 5001-10000

   ☐ Between 10001-15000

   ☐ Over 15,000

9. Type of homestead

☐ Semi-permanent house

☐ Permanent house

10. Distance to health facility(JOOTRH)

☐ Less than 1km

☐ 1-2km

☐ 2-4km

☐>4km

11. Means of transport

☐ Bicycle

☐ Motorbike

☐Matatu

☐ Private car

PART 2: CERVICAL CANCER SCREENING

1. Prior Pap smear

☐ Yes

☐ No

PART 3: SEXUAL AND REPRODUCTIVE FACTORS

1. Age at first sexual debut _____
2. No. of live sexual partners ☐ 1-2 ☐ 3-4 ☐>4
3. Current partner circumcised ☐ Yes ☐ No
4. No. of pregnancies (parity) _____
5. No. of live births _____
6. No.of miscarriages _____
7. History of unwanted pregnancy ☐ Yes ☐ No
8. History of STIs
    a. Syphilis ☐
    b. Gonorrhea ☐
    c. Chlamydia ☐
    d. Herpes ☐
    e. Others ☐ _____

9. Type of family planning

    a. Injectable

    b. Oral contraception

    c. IUCD

    d. Implant

    e. Others

PART 4a: MEDICAL HISTORY & RISK FACTORS

1. Alcohol ☐ Yes ☐ No

2. Smoking ☐ Yes ☐ No

3. Substance abuse ☐ Yes ☐ No

4. History of chronic illness

☐ Diabetes

☐ Hypertension

☐ Asthma

PART 4b: HIV-RELATED RISK FACTORS

1. Time of diagnosis _____

2. Stage at diagnosis

    ☐ I

    ☐ II

    ☐ III

    ☐ IV

3. Duration of HIV infection

☐<5 years

☐ 5-10 years

☐>10 years

4. Opportunistic infection

a. Meningitis ☐

b. TB ☐

c. Kaposi sarcoma ☐

d. Others ☐

5. Discordant couples ☐ Yes ☐ No

6. Last CD4 Count

☐<200

☐ 200-350

☐ 350-500

☐>500

7. Viral load

☐<1000

☐ 1000-10000

☐>10000

8. Use of ART Therapy ☐ Yes ☐ No

9. Adherence to ART☐ Yes ☐ No

10. Support center ☐ Yes ☐ No

Appendix II: Dummy Tables

Study population

SECTION A

Variable	ICC N=100	No ICC N=100	P value
SOCIODEMOGRAPHIC FACTORS	Mean (SD) N (%)	Mean (SD) N (%)	
Age Gender Education level Marital status Employment status Household monthly income Type of homestead Distance to the health facility Means of transport			

SECTION B, C, D

Variable	ICC N=100	No ICC N=100	Crude O.R	P value
CERVICAL CANCER SCREENING				
Cervical cancer screening (Pap smear)				
REPRODUCTIVE RISK FACTORS Age at first sexual debut, No.of life sexual partners, Currentpartner circumcised, Parity, No.of live births, No. of miscarriages, History of unwanted pregnancy, History of STIs, Family planning				

MEDICAL AND HIV-RELATED RISK FACTORS Alcohol intake,Smoking,Substance abuse, History of chronic illness, Time of diagnosis, Stage at diagnosis Duration of HIV infection, Opportunistic infection, Discordant couples, CD4 Count, Viral load, Use of ART Therapy, Adherence to ART, Support center, Primary care provider				

SECTION E: ADJUSTED

Variable	OR	aOR	P-Value
Cervical Ca Screening			
Reproductive risk factors			
HIV related risk factors			

Appendix III: KNH-UON ERC Approval Form

(*Will be attached here*)