SCHOOL OF PUBLIC HEALTH
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CERVICAL DYSPLASIA AND ASSOCIATED RISK FACTORS AMONG HIV –INFECTED WOMEN ATTENDING HANDS –CARE CENTER IN BRIKAMA,THE GAMBIA

BY

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DECLARATION

I**, Anna H. Jammeh**, declare that except for other people's research which have been duly acknowledge, this thesis is the result of my original work undertaken under supervision and that it has neither in whole nor in part been presented for another degree in this university or elsewhere.

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DEDICATION

Dedicated to my late father

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I would like to thank the Almighty God for his guidance.

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ABSTRACT

Background: Cervical cancer is the second most common cancer worldwide after breast cancer and is an example of a disease of global inequity in health as majority of the deaths occurs in sub-Saharan Africa. With the increase in HIV pandemic, its incidence has increased three fold .In the Gambia, the true burden of cervical dysplasia in HIV infected women is not known and this shows an important gap in the management of cervical cancer and HIV.This study aims to determine the burden and associated risk factors of cervical dysplasia in HIV infected women attending Hands-on –care Medical Centre at Brikama, The Gambia.

Method: A cross-sectional quantitative study was conducted at Hands-on –care center in Brikama, The Gambia on HIV- infected women between the ages of ≥18 years and ≤60 years. Patients were selected using a systematic random sampling from the out-patient department. A standardized questionnaire was used to interview, hospital records were reviewed and visual inspection with acetic acid (VIA) screening was also done. Data was analyzed in STATA 13.0. Descriptive statistics were used to determine prevalence, chi-square test of proportions and multiple logistic regression models were used to test for level of significance between cervical dysplasia and the associated risk factors.

Findings: A total of 322 HIV infected women were interviewed and screened, the mean ages (±SD) were 39(±8.0) years. The prevalence of cervical dysplasia was 22 %(70/322). Significant risk factors associated with cervical dysplasia in this study were age group 26-35 years (OR:2.7; 95% CI:0.3-23.6 ;p-value: 0.02),first sexual intercourse at ages between 16-20 years(OR:2.7 ;95% CI :1.2-6.1 ;p-value:0.001) , first birth between 16- 20 years (OR: 0.4 ;95%CI :0.2-0.8 ;P-value: 0.002) and having 4 or more children(OR:16.6 ;95% CI :2.2-124.4 ;p-value:0.002).

Conclusion: cervical dysplasia is a problem in HIV infected women seeking care at Brikama Hands-on care. Age group between 16-20 years at first sexual intercourse and birth, increased parity and middle age woman are significant risk factors, therefore screening is recommended for HIV infected women seeking health care at Hands on care medical center.

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AIDS-	Acquired immunodeficiency virus
CD4+	cluster of Differentiation
CDC-	Center for Disease control
CIN-	Cervical Intra epithelial Neoplasia
DNA -	Deoxyribonucleic acid
EPIC-	European prospective investigation into cancer and nutrition
HAART –	Highly Active Anti-retroviral Therapy
HOC-	Hands –on -care
HIV -	Human Immunodeficiency Virus
HPV -	Human Papillomavirus
HSIL -	High grade Squamous Intra epithelial Lesion
IACR-	International Agency for Research on Cancer
ICC -	Invasive Cervical Cancer
LEEP -	Loop Electrosurgical Excision Procedure
LMIC-	Low and middle income countries
LSIL -	Low grade Squamous Intraepithelial Lesion
SIL-	Squamous Intra epithelial Lesion
SCC-	Squamous cell carcinoma.
SSA-	Sub-Saharan Africa
VIA-	Visual inspection with acetic acid
WHO-	World Health Organization

CHAPTER ONE

INTRODUCTION

1.1Background

Cervical cancer is the final stage of a continuum of consecutive stages of which begins with the precursor lesions of cervical dysplasia or cervical intraepithelial neoplasia and ends in the invasive or disseminated form of cervical cancer. It is a disease which grows slowly and takes a long duration to manifest its symptoms. It is mostly caused by human papilloma virus infection. The malignant lesions begin from the cervix and spreads to distant parts of the body. It is considered a preventable disease due to its long pre-invasive state and therefore screening can be performed to prevent its onset (WHO 2014). Human Papillomaviruses are easily transmissible and highly prevalent, and it has been demonstrated as one to be the most frequent and sexually transmitted infection(Wang & Cui, 2016). HPV cannot be treated once acquired but vaccines can be administered before commencement of sexual activity to prevent infection.While there are numerous types of HPV viruses, only a few have been associated or known to cause the disease(Wang & Cui, 2016).Majority of women are exposed to HPV during the course of their lives, but a small number are unable to eliminate the virus and its persistent exposure to the high risk type which causes the development of premalignant lesions(Mahesa, 2012). The human cervix is located in the lower part of the uterus which is lined by squamous epithelial cells and has a transformation, which is the region susceptible to HPV adherence.

Cervical intra-epithelial neoplasia (CIN) is shown by the presence of cytological atypia and disturbances of cellular maturation and stratification. The lesions range from a well differentiated intraepithelial neoplasm (CIN1) to a poorly differentiated intraepithelial neoplasm (CIN3).CIN 2 occupies an intermediate position(Menon, Rossi, Harebottle, Mabeya, & vanden Broeck, 2016). Studies have also shown that for the approximate and

likelihood of a CIN 1 regressing is 60%, progression to a CIN 3 is 10%, and the progression to an invasive cancer is 1% whilst for CIN 2 are 40%, 20%, and 5%, respectively(Arends, Buckley, & Wells, 1998).

Factors relating to sexual behavior have also been associated to cervical dysplasia and its precursors. HPV infection is mainly related to patterns of sexual behavior and sexual activity which includes multiple sexual partners, early age at first coitus, promiscuous male partners and lack of condom use(Castellsague & Munoz, 2003) (Mahesa, 2012). In addition, other factors include parity, smoking, diet, use of oral contraceptives and immunosuppression/HIV. Since HPV is important in the development of both CIN and an invasive cervical cancer, the risk factors for getting infected with a high risk oncogenic HPV type are indirect risk factors for both the precancerous lesions and invasive cancer of cervix (Mahesa, 2012).Cervical cancer in addition to Kaposi sarcoma and to non-hodgkin's lymphoma have been classified as AIDS- defining lesion by the CDC due to the risk of developing these cancers in the presence of HIV(Mbulaiteye, Bhatia, Adebamowo, & Sasco, 2011).Women who are infected with HIV are usually five times higher than the non-HIV infected to harbor the HPV and also for the disease to progress to malignancy. The prevalence of the high risk-HPV and of a genotypic distribution varies in a different geographic area(Akarolo-Anthony et al., 2013).

1.2 Global burden of cervical cancer

In the year 2012,Cervical cancer was estimated as 528,000 newly diagnosed cases per year and is the fourth overall cancer affecting most women worldwide, after the breast, colorectal, and lung cancers, 70% of the world's burden occurs in resource low countries within the sub-Saharan continent and it is fourth overall cause of all cancer related death (266,000) (GLOBOCAN 2012).

Every year, about 494,000 women globally would develop cervical cancer and of which about 49.5% die from the disease annually of which about 80% are in low income countries (WHO 2008).It is estimated that between 2012 to 2025,new cases in third world countries will rise from 444,546 to 588,922 (Abiodun, Olu-Abiodun, Sotunsa, & Oluwole, 2014).About 530,000 new cases were reported worldwide, and approximately 275,000 deaths occurred of which 7.5% were reported in poor resource countries (farlay J 2008).Estimates indicated that 80% of annually diagnosed women live in developing countries and about 96% of women have not been screened before (Murugi, 2014).

In 2012 it was indicated that around 1,401,400 cervical cancer cases were diagnosed over the five year period in the year 2000 as compared to breast cancer which accounted for 3,860,300 and of these more than half are in the third world countries, this shows even though breast cancer is on the rise ,cervical is a cause of high morbidity and mortality(WHO 2002.).The regions with high risk per 100,000 women population includes East and West Africa with an ASR > 30/100,000, Southern Africa has 26.8/100,000, South America 23.9 lastly Middle of Africa 23.0/100,000 respectively (Ibrahim et,al 2013).The cancer is an example of a disease of global inequality in health, as it peaks between 35-45 years of age during the prime period of a woman's life. Death from cervical cancer in the first world countries is substantially lower than in third world nations due to the availability of prevention, early detection, and treatment services. In third world countries only 5% of the women have ever been screened as compared to 40-70% in first world countries.

1.3 Cervical cancer burden in Africa

A lack of precise information about cancer magnitude in the African setting is due to limited cancer registries which masks the picture of the cancer problem in this continent.

Therefore the burden of disease is frequently estimated based on average data from developed countries.

The extent of cervical cancer has been underestimated and not considered as a priority in low income developing countries as compared to other diseases like tuberculosis , malaria and HIV/AIDS.In 2010, Africa was estimated to have 78 ,897 who were clinically diagnosed with the cancer as annually and 78% died from the disease, which verily showed a higher incidence to mortality ratio as compared to USA, 13,162 and 5,214women are diagnosed annually and die annually from the disease respectively out of 121.32 million women of 15 years and more, there it is the 4th most common between 15-44years in women(Denny, 2010). .

Table 1: Age standardized cervical cancer incidence and mortality rates worldwide

World Area	Incidence per 100,000	Mortality per 100,000
Eastern Africa	**34.5**	**25.3**
Western Africa	**33.7**	**24**
Southern Africa	**26.8**	**14.8**
South – Central Asia	24.6	41.1
South America	24.1	10.8
Melanesia	23.7	16.6
Middle Africa	**23**	**17**
Central America	22.2	11.1
Caribbean	20.8	9.4
South – Eastern Asia	15.8	8.3
Central and Eastern Europe	14.5	6.3
Micronesia	13.4	4.9
Eastern Asia	9.6	3.9
Northern Europe	8.3	2.4
Southern Europe	8	2.6
Western Europe	6.9	2
Northern Africa	6.6	4
Australia/New Zealand	5	1
Western Asia	4.5	2.1

Extracted from GLOBOCAN 2008(Age standardized ratio).

Researches have shown some significant differences in the age-standardised ratio with incidence rates (ASIR per 100,000) in the different regions of Africa. An ASIRs of 42.7was reported in eastern Africa, whilst 28 and, 12.1 were reported in middle and northern , southern and western reported 38.2 and 29.3 in respectively(Denny, 2010).

1.4 Cervical cancer burden in the Gambia

In the Gambia, cervical cancer is the leading gynaecologic cancer related cause of admissions and the number two cause of all the cancer deaths among women after breast cancer and with an estimated population of 549,836 women of 15 years and older at a risk of developing the disease. Currently the estimates indicated that annually 98 new cases are diagnosed of which 57 die from the disease (Bruni et al., 2016) .According to GLOBOCAN 2012 ,the incidence and mortality estimated per 100,000 (age stratified for women) was 26.2 and 18.0 respectively (Ferlay et al., 2015).In the Gambia ,cervical cancer is common among all women in the population and second most common between the ages of 15-44years in women. The true incidence of the cervical cancer and the current HPV burden in The Gambia is not known as there is gross under-reporting, and some of the figures are health facility-source data.However, Gambia belongs to the West African in which the percentage of women harbouring the cervical HPV -16and 18 is estimated to be 4.3% of the general population whilst 56.7% of the invasive form of cervical cancer are also linked to these same HPV serotypes(Bruni et al., 2016).

Cervical cancer causes a lot of social, psychological and financial burden, a disease most especially affecting the poor and those with low educational status in whom the risk factors are mostly prevalent and prevention includes regular screening of all sexually active and 25 years and above women through HPV test, pap smear and visual inspection with acetic acid (Abiodun et al., 2014).

Women infected with the HIV tend to have higher rates of been infected with the human papillomavirus (HPV) than the women who are not infected, and are also at a higher risk for persistent infection and a rapid progression to malignancy. In addition, HPV may be a cofactor in acquiring HIV and persistent infections with the high risk HPV are also known to be a necessary first step of cervical dysplasia. The number of the high risk-HPV infection and of genotype distribution varies in a different geographic area.

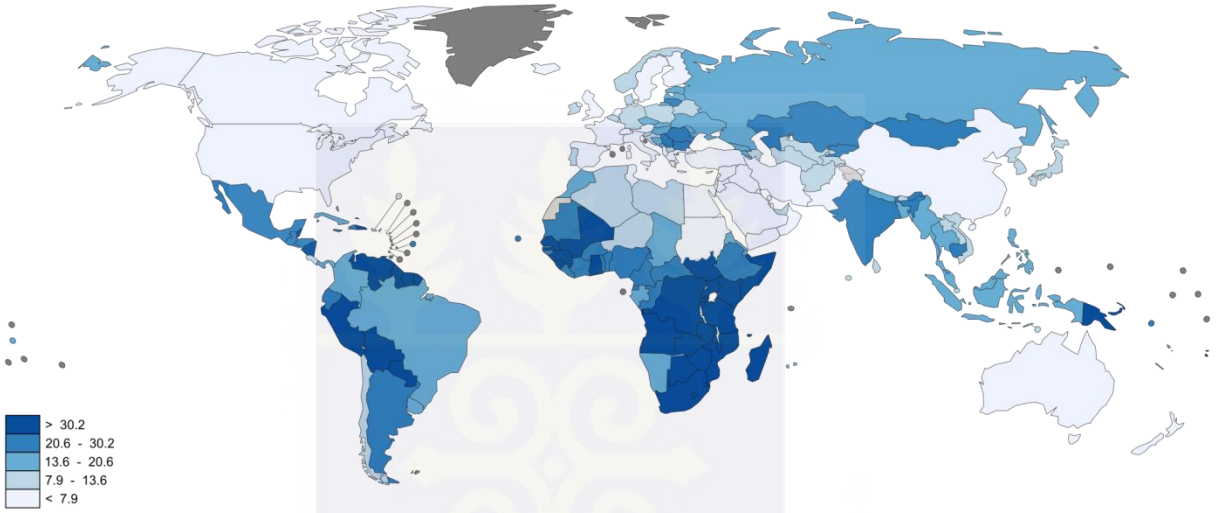

Figure 1: Estimated age -standardized rates of cervical cancer incidence (Adapted from GLOBOCAN 2012)

In the development of a pre invasive cervical lesions and its progression to the invasive stage, it is confirmed that "high-risk" specific types of the vertically transmitted HPV play a role in the development process. Earlier researches have shown that those with severe immune-depression due to HIV have a risk of getting infected with HPV and cervical intraepithelial neoplasia(CIN)(Hawes et al., 2003)..

A study done in Nigeria (Abuja) on HIV infected women with cervical cancer risk showed that out of a total of 2501 participants ,the prevalence was 6% for pre-cancer and cancer and these results were lower than most previous reports from other

studies.(Ellerbrock et al. 2013).Another study in Ivory Coast has shown that HIV- 2 was associated with invasive cervical cancer. Although not much information is known about the relationship between the HIV viral load (decreased CD4 count) and invasive cervical cancer, verification of these relationships is necessary for the planning and implementation of cancer–prevention programs among the HIV-positive women(Hawes et al., 2003).

It is known that developing CIN is truly increased in HIV infected women, this is as a result of immunosuppression caused by the HIV virus and finally the inability to control the production of HPV oncogenes. This phenomenon allows the continued production of oncogenic proteins E6 and E7, which are so central to the pathogenesis of the cervical cancer.

The prevalence of the SIL in the HIV positive group varies from one study to another. Women infected with HIV who have Low-grade squamous intraepithelial lesion are at increased risk of its progression to the high-grade type and the invasive carcinoma(Vafaei, Asadi, & Foroughinia, 2015). Despite decline in the prevalence and mortality, it is still the third cause of all cancer related deaths among women in the world. Other risk factors that are associated with the cervical cancer, including smoking, parity, race, the use of oral contraceptives, and sex at an early age, multiple sexual partners, immune deficiency due to HIV infection, and low socioeconomic status.

1.5 Problem statement

Cancer of the cervix is the second most common overall cancer among the women worldwide and the second after breast cancer, of approximately 528, 000 new cases in 2012 out of which about 87% (376,000) occurred in developing countries and an estimated 266,000 deaths reported (GLOBOCAN 2012). In Western Africa, about 28, 903 new cases of the cervical cancer were recorded yearly (Ico, 2016). Currently the estimates from

ICO,2016 indicate that 98 women are diagnosed yearly and of which 57 die from the disease (Bruni et al., 2016) . In the Gambia, cervical cancer is the first cause of gynecologic cancers in women between15-44years of age and the second most common in the general population of women after breast cancer. But in Western Africa,an estimated percentage of about 4.3% of the women are said to harbor HPV-16 or18 at any given time, and 58% of the invasive cancers are linked to HPVs 16 or 18 (Bruni et al., 2016). WHO has recommended cervical cancer screening programs with or without HPV testing as ways of effectively lowering both disease incidence and mortality (WHO 2001).Screening is however available in a few major health facilities in the Greater Banjul Area. Screening for premalignant lesions using Visual inspection with acetic acid in the HIV infected women have been less investigated in The Gambia and less than 3% of the women have ever been screened. The lack of a cervical cancer registry in the country proves that there is inadequate information and no data on the current prevalence of cervical dysplasia in the HIV women in the Gambia, and its associated risk factors. Since 90% of cervical cancer cases cannot be treated in most of the country's health facilities because most women present late or in advanced stages of the disease and the only treatment option available is chemo- radiation (chemotherapy and radiotherapy) which is not available in the country. Multiple studies have shown that cervical dysplasia or cancer is caused by HPV and associated with several risk factors such as; behavioral ,reproductive and clinical risk factors for any cervical dysplasia to progress into cancer and based on what is known, it has been confirmed that the cervical cancer can also be prevented through the early detection and screening of women .In the Gambia cervical cancer screening uptake remains low as compared to other countries and therefore the prevalence, and other risk factors associated with the disease are not known.

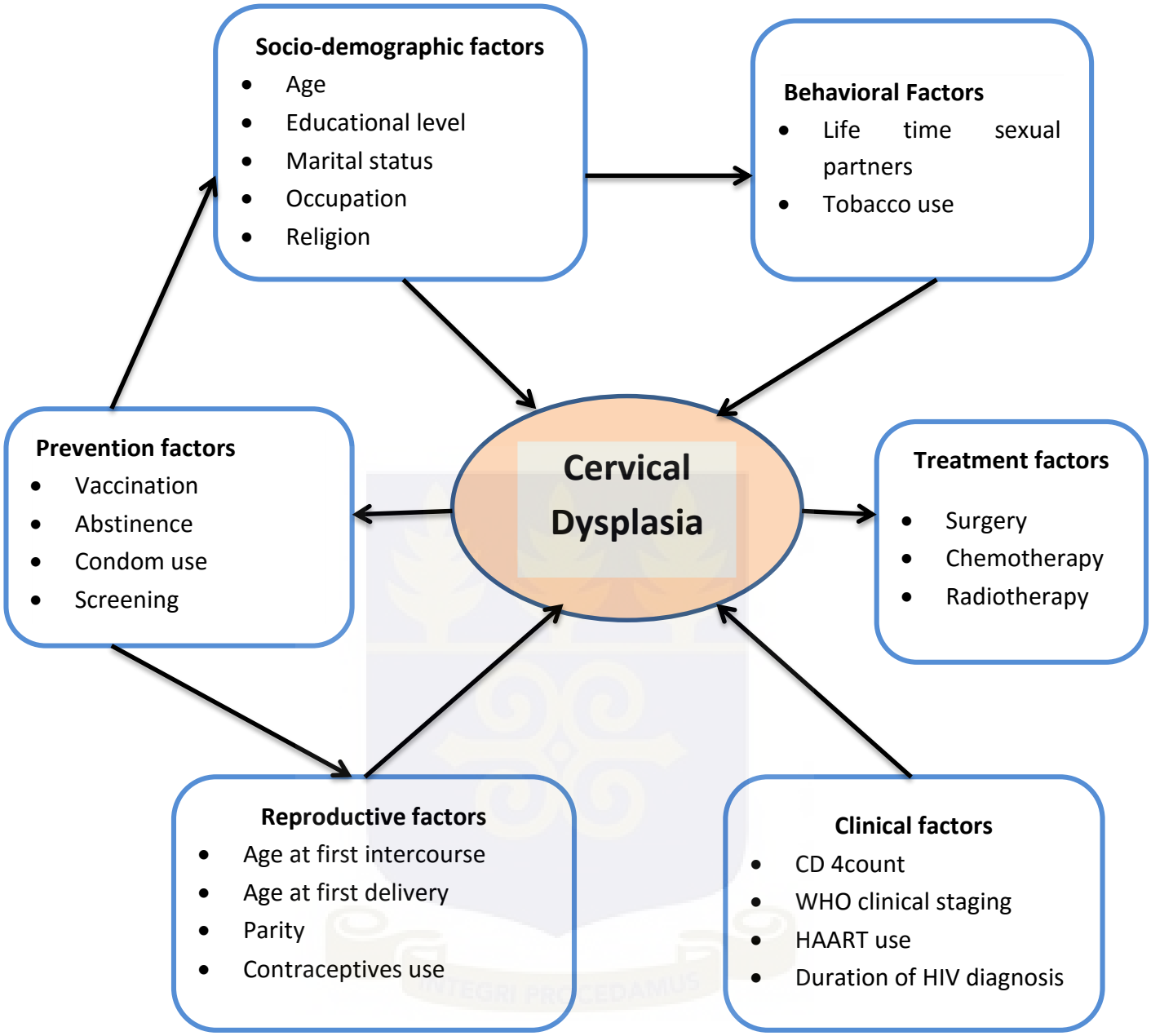

Figure 2: Conceptual framework

Cervical cancer is a global burden as most morbidities and mortalities are higher in sub-Saharan Africa. The most common risk factors are HPV and HIV infection. The HPV is a sexually transmitted infection and in the presence of the persistent cervical infection with the hrHPV has been known as a necessary but not sufficient cause for the commencement of dysplasia in women. Studies have demonstrated that the infection with HPV follows the

development of the cancer by several decades and that persistent infection is necessary for the development and progression in the cervix, either to higher grades of pre-cancerous disease or to invasive cancer form.

The Socio-demographic including the age, marital status, educational level, religion and occupation have been found associated with higher rates of cervical dysplasia. Women with low socio-economic status or income are less likely to have access to and attend screening services which increases the risk of developing precancerous lesions or dysplasia

Behavioral risk factors such as HPV infection, multiple sexual partners and tobacco use causes an increased risk of the acquisition and the persistence or reactivation of the infection with the HPV ,as they weaken the immune system and subsequently leading to the development of a precancerous lesions or cervical dysplasia. Majority of Cervical abnormalities in the HIV women (low CD+4) are as more likely to be very severe, more aggressive and resistant to the treatment than HIV negative women.

Reproductive factors such as prolonged use of the oral contraceptives, high parity, early age at sex and early age at delivery increases the risk of cervical dysplasia, as recurrent trauma to the birth canal causes an exposure to the HPV virus and also the prolong use of oral contraceptives causes changes in the epithelial lining of the cervix by the hormones and as it does not provide any barrier effect to the cervix for the prevention of HPV exposure.

Prevention factors such as vaccination, condom use, abstinence and regular screening are affected or determined by the implementation of policies such as free vaccinations to all under aged girls, the availability of condoms for public use and free screening services to all women. Also the prevention factors will help in the inhibition of the development of

cervical dysplasia or precancerous lesion and the effectiveness of the prevention factors will be aided by increase knowledge or awareness level of the disease in its causative agents, mode of transmission and ways of prevention both primary and secondary prevention, effective to the health of individual and the society at large.

1.6 Justification

Despite the high level of the incidence of cervical cancer, attention focused to it is low compared to breast cancer and its prevalence is been exacerbated by HIV/AIDS pandemic. Currently cervical cancer incidence accounts for about 17.6% of all cancers reported in the country (GLOBOCAN 2012). High morbidity and mortality rates are due to lack of adequate screening centers, and also presentations of cases in the advance stage of the disease. The cervical cancer prevention and control strategy includes health promotion such as (lifestyle modification, safe sexual behaviour, health education on tobacco and excess alcohol consumption) and primary prevention (HPV vaccination, cancer screening, early diagnosis and treatment).

The estimated burden is 4.3% what is unknown is the true burden of cervical dysplasia, and invasive cervical cancer in a high risk population as that of the Gambia is a matter of great concern, especially with the current high HIV/AIDS prevalence. This emphasizes the need to conduct a study on the prevalence of the cervical dysplasia and its associated risk factors in HIV infected women. Previous studies have shown the need for cervical screening in the HIV women because of the increased risk of CIN and invasive form among the people living with HIV/AIDS.

The findings from this study will inform both health specialists and policy makers of the need to focus on effective health education and screening of all HIV infected women,

which is the practical method for settings with no universal national HPV vaccination coverage like The Gambia.

Finally, very little or no information is available about the current prevalence of the cervical dysplasia in HIV infected women in the Gambia. This study will therefore provide baseline information on the current prevalence.

With good policy formulation, HIV-infected women would be encouraged to have good health seeking habits including regular screening for cancer of cervix and in so doing pre-invasive cancer will be detected and treated on time.

1.7 Research questions

1. What are the risk factors associated with cervical dysplasia in the HIV infected women attending Hands on care clinic in the Gambia?

2. What proportions of VIA positive are screened at Hands on care medical centre in the Gambia?

1.8 Objectives

1.8.1 General objective

The general objective of this study are to determine the prevalence of cervical dysplasia or premalignant lesions through visual inspection with acetic acid(VIA) in HIV infected women attending Hands on Care medical centre in Brikama.

1.8.2 Specific objective

The specific objectives of this study are;

1. To determine the proportion of Cervical dysplasia in HIV infected women.
2. To determine socio-demographic risk factors associated with cervical dysplasia in HIV infected women
3. To determine reproductive risk factors associated with cervical dysplasia in HIV infected women
4. To determine the behavioural risk factors associated with cervical dysplasia in HIV infected women
5. To determine the clinical risk factors associated with cervical dysplasia in HIV infected women

CHAPTER TWO

LITERATURE REVIEW

Cervical cancer is a disease which usually affects many women and contributing to avoidable high levels of morbidities and mortalities. About 85% of the global burden occurs within the less developed countries and accounts for almost 12% of all of female cancers, it is also the leading female malignancy and the number one cause of cancer death, especially among the middle- aged women. In most developing countries however, cervical cancer is ranked as second to cancer of the breast, contrarily in developed countries it is fifth (parkin DM.1990). About 530,000 new cases were reported worldwide, and 275,000 deaths occurred of which 7.5% were reported in poor resource countries (farlay J 2008).

In the year 2000 , a global prevalence was estimated as 1,401,400 of diagnosed cervical cancer cases as compared to breast cancer which was 3,860,300 and of which about 1 ,064, 000 and 1, 522 ,000 are in developing countries respectively(WHO 2002.) This wide gap is due to inadequate or unavailability of the effective screening that aids in the early detection and timely treatment(IARC, 2013).Most of the women, who die from the cervical cancer, are in the productive stages of their life, during which they are involved in the family management and also contributing to the social and economic life of the community(WHO Guide2006).

2.1 Etiology and pathology

The known cause and also a risk factor of cervical cancer in women is the persistent infection with the hrHPV. Infection with the HPV is common sexually transmitted infections today and there are more than 100 different genotypes of HPV. The DNA of the HPV virus can be found in other parts of the body different from the cervix such as oral

mucosa of both men and women, anal mucosa of sexes, vaginal mucosa, foreskin, and scrotum and glands penis.Infection occurs through an abrasive surface of an infected with an uninfected epithelium. In most people, there a no clinical symptoms or signs of HPV infection only a few the the infection persist leading to cervical cancer (Denny, 2010)

Some genotypes are considered high risk (oncogenic) because they are associated with the invasive cervical cancer, vulva, penis, anus, and others. Among them are genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 and 82 (CDC 2007).

The two hrHPV genotypes are associated with the cervical dysplasia. After the year 2000,the HPV virus was confirmed as the main etiological factor of cervical cancer and is the only cancer with a clear viral etiology (Behtash et al.2003) .It has now been proven to be a factor in the onset of cervical cancer, and it is suggested that the worldwide prevalence of the HPV infection among cervical cancer cases is as high as 99.7 % (Mahesa, 2012).In a retrospective study to determine the presence of hrHPV DNA general primer GP5+/6+ PCR in the databases of 57 women who had developed cancer showed that the presence of hrHPV leads to abnormal cytological results in women with cervical cancer(Zielinski et al., 2001).Also another study showed that cervical malignant tumors are directly associated with hrHPV and that certain malignant cervical tumours phenotypes correlate with specific HPV types (Zehbe & Wilander, 1997) .Various studies have also shown that the variation in the geographical area or land mark also differs with the type of HPV.A study conducted in Vietnam(Can Tho) showed that HPV type 58 and 52 were commoner in the women screened(Lan, 2012).In Brazil HPV-16, 58, 31 and 18 were 49%, 13%, 12% and 4.5% respectively were the most common(Camara et al., 2003). A study in Mali also showed 96.9% of all the cases had HPV DNA and types 6,18 and 31 were the most common types(S. et al., 2002).

However, additional factors increase both HPV persistence and the risk of the progression from pre-malignant lesion to the invasive cervical cancer, such as immunosuppression from any cause, including HIV virus infection and malnutrition, smoking, high parity ,oral contraceptives use , sexual behaviour (polygamy, promiscuity, early sexual intercourse) and co-infection with other STIs. A recent study showed that cervical cancer was rare among catholic nuns. Risk was also found to be higher among women who married early. Cohort studies have shown that the cancer stems from HPV infection through a very long latency period and vertical transmission is the predominant method. Different research methods have proven that the HPV can be detected in 95%-100% of specimens of cervical cancer. Abnormal cellular changes in the cervix are referred to as dysplastic or carcinoma-in-situ. In both stages, cells change in appearance, shape, size, or rate of growth but, the primary distinguishing pathological characteristic between dysplasia and carcinoma-in-situ is that dysplastic cells may regress to normal cells or progress to cancer(Beining, 2012).Cervical dysplasia is also known as cervical Intraepithelial Neoplasia or Squamous intraepithelial lesions. Precancerous lesions are lesions that have the ability to progress to invasive cervical cancer if left untreated.

In addition data on the natural history of dysplasia is scarce, as these lesions are normally treated but studies have shown that regression is a component in the natural history of dysplasia.

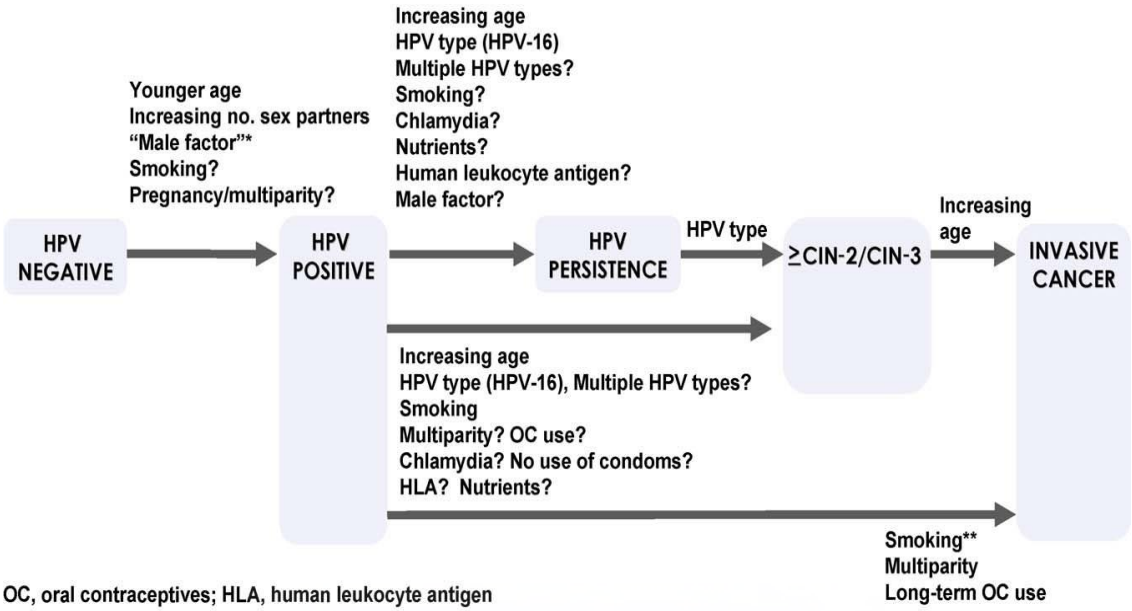

Figure 3: Over view of the natural history of cervical cancer

2.2 HIV and cervical dysplasia

The development and progression of cancer due to the presence of the HPV and HIV infection has led to the recognition of cervical cancer as an AIDS defining lesion in the HIV women. This is due to the fact that HIV infected women manifest cervical symptoms earlier secondary to low immunity and their lives are shorten due to disease complications than the HIV negative women. The incidence in the HIV positive women is five times more than in HIV-negative women .The Invasive form of cervical cancer is about three times commoner in the HIV-positive women than in HIV negative women. The HIV seropositivity and a low CD4+ count are the strongest predisposing factors for the persistence of HPV DNA. Cervical intraepithelial neoplasia development is associated with HIV infection and a high HPV viral load, most especially in severely immunosuppressed women, and this could be due to the reactivation of HPV virus. Studies have supported this evidence and it showed that the plasma HIV RNA

(Ribonucleic acid) titers and the CD4+ counts are the determinants of the ability to easily detect HPV. Additionally, the Highly Active Antiretroviral Therapy does not seem to have an impact and or persistence of HPV infection in this population. Available data has suggested that the widespread use of the HAART has not shown a decreased prevalence of the genital HPV-infection in HIV-positive patients (kayumba, 2010).Studies have also shown that HPV infection is usually transient in HIV negative women whilst in HIV infected women or immunosuppressed, the persistence of HPV is higher and the dual occurrence leads to the shortening of the progress of infection from cervical dysplasia to cervical cancer.

Persistent HPV infection causes a prolonged exposure to the oncoproteins E6 and E7 that interferes with the host's cell-cycle control and leads to accumulation of the abnormal cells that are central in the pathogenesis of cervical cancer. HIV infection causes the alteration of cervical carcinogenesis and as a result HIV infected women are often seen with advanced forms of cervical cancer at a very young age as compared to the others.

As more resource-limited countries develop the infrastructure to provide clinical care and antiretroviral therapy to reduce the immediate mortality risk of AIDS, effective cervical cancer screening programs that address the unique biological relationship between HIV, CIN, and cervical cancer are needed(Woo et al., 2013).A retrospective study in Tanzania concluded that precancerous lesion's prevalence in HIV positive women was 71.8% whilst the HIV negative were 27.3% ,also invasive cervical cancer prevalence was 8% in the HIV sero-negative women and 11% in the HIV-positive women(Chambuso, Shadrack, Lidenge, Mwakibete, & Medeiros, 2017).Abel et al also reported that the prevalence of precancerous lesions was significantly high (22.1%)(Gedefaw, Astatkie, & Tessema, 2013).

Massad et al.,(1999) had reported a prevalence of 38.3% of abnormal cytology in HIV women as compared to 16.2% in HIV uninfected women. The significant findings in the HIV infected women included both High-grade lesions and low-grade also the significant risk factors included< 200 cells/µL CD4, HPV viral DNA and also a previous history abnormal cytology(Massad L S et al 1999.).

Ahdieh et al., (2000) demonstrated that the risk of CIN as related to HPV persistence in a case control study on HIV infected women, 13.4% as compared to 2.4% respectively.

Thomas et al. (2001) conducted a cohort study in Thailand among sex workers and showed that women who were both HIV and HPV infected were 20 times higher to develop high grade lesions than the HIV negative women.

Ellerbrock et al, (2000) also demonstrated that the HIV women were 4.5times more likely to develop CIN within 54 months of follow-up interval as compared to the HIV negative women. Among HIV infected in the exposure group, those with transient HPV , the persistent HPV types other than 16 or 18 were all significantly associated with CIN.

A study in a South African hospital (case-control) has also concluded that risk of developing a cervical cancer and vulvar cancer in HIV women were 1.6 and 4.8 times higher than HIV negative women respectively. But contrary to this study, Rwanda, South Africa and Uganda had shown that the invasive form of cervical cancer was not related to HIV exposure as it 0.8 times protective (Sitas et al., 2000).

A study conducted by Selik and Rabkin (1998) found that the HIV women were 5.5 times more likely to develop the cervical cancer.

A study in Korea by park et al has shown that the prevalence of hr-HPV and abnormal cervical cytology was 30% and 18.3% respectively and both were statistically significant

as compared to the HIV uninfected group which was 4.9% and 1.8% respectively(Park et al., 2014).

Similarly another comparative study conducted in Iran, on HIV infected women, female commercial sex workers and the general population of women has shown that the risk of one developing cervical infection was 5times higher in both groups as is compared to the general population and frequency of abnormal cervical cytology was 6.8 times higher in both groups (Vafaei et al., 2015).

Another study conducted in southern Israel to know the HPV prevalence and cytology abnormalities in HIV infected women has shown that of the 58.3%(49) of the study participants who were HPV-positive; 34 had oncogenic genotypes, 17 had abnormal cytology and 21 referred for colposcopy (Leibenson et al., 2011).

WHO/ICO (2010) stated other associated cofactors which contribute to the progression of cervical dysplasia from cervical HPV infection include tobacco smoking, high parity, early age at sex and co- infection with HIV (WHO/ICO, 2010). In resource poor countries, a major issue is co-infection with HIV and HPV with 20% of HIV women screened for cervical cancer(Wanjiru Mbatia 2016)

Multiple sexual partners increase the risk of developing sexually transmitted infections, a study done in morocco showed that polygamy which is related to multiple sexual partner increases the risk of cervical cancer(Maamri, El-Hfid, Chafi, & Boutayeb, 2012).

2.3 Risk factors

2.3.1 Socio-demographic risk factors

Sociodemographic factors has been defined in different ways in previous researches, it includes; educational level, marital status, type of marriage (polygamous, monogamous),

occupation, religion and ethnicity. Cervical cancer is associated with risk of a low educational level. A population based study showed socio-economic status which was measured by a woman's level of education, showed that low class or illiteracy to be highly associated with the cervical cancer (Parikh, Brennan, & Boffetta, 2003)

Similarly in another study, it was found that higher education was a less risk factor to cervical cancer, showing an OR of 0.18. Most likely a low educational status causes an increase in intercourse at an early age, sexual partner and high parity(Reis, 2011).Behavioral risk factors such as promiscuity or multiple sexual partners, prostitution are highly common in women with low socio-economic status.

2.3.2 Reproductive risk factors

Reproductive characteristics such as age at first sex, age at first delivery, parity and use of contraceptive have been categorized as risk factors for one to be exposed to the causative agent for cervical cancer (HPV). Early engagement in sexual intercourse may predispose one to have early pregnancy, multiple sexual partners and exposure to STIs (Rweyemamu,karugira yofasi 2003.). High parity predisposes a woman to hormonal carcinogenesis and birth trauma which in turn makes it susceptible to the HPV. It has been stated that HPV infection is a crucial factor for the commencement of cervical cancer, however, the infection with HPV alone may not be adequate for it to progress to cancer but other factors must be present in conjunction with the virus for it to progress into cancer. Oral contraceptive use has been associated with cervical cancer but not in all though. A study done by IARC showed that oral contraceptives use for more than 5 years was associated to cervical neoplasia(OR3.4; 95% CI2.1 to 5.5)(Moreno et al., 2002) .Increased number of term pregnancies has been associated cervical cancer. The risk of developing cervical cancer in the women who had seven or more pregnancies was four times.

During pregnancy, the repeated hormonal changes which occur (estrogen and progesterone)alters the immune system which directly influences the HPV persistence and High parity distorts the transformation zone due to repeated birth traumas ,facilitating exposure to HPV .

2.3.3 Behavioral risk factors

Smoking has long been associated with cervical cancer as carcinogenic substances are said to destroy the cervical mucosa causing dysplasia on the cells and once in the presence of HPV, it progresses easily to cervical cancer. The hypothesis that there is a mutual interaction between cigarette smoking and HPV has been showed in the cervical mucus of the smokers. Of more recently, the malignant changes of the HPV16 in immortalized endocervical cells by the cigarette smoke has been evidently proven(Castellsague & Munoz, 2003). Many descriptive studies have regularly showed that the risk of progression from dysplasia to cervical cancer may be influenced by tobacco smoking(Roura et al., 2014) Though the (IARC) classified smoking as a cause of cervical cancer ,it is still not clear as evidence of causal factor in the absence of a HPV infection, as most of the researches were done retrospectively .A study done by EPIC in assessing the association of smoking and risk of CIN 3,carcinoma in situ and the invasive cervical cancer has confirmed that smoking is a risk factor (Roura et al., 2014).

In an analysis of IACR multi centric case control study showed that tobacco increases the risk of cervical cancer among the HPV positive women(Plummer M, Herrero R, Franceschi S, 2003).

It is stated that multiple sexual partners is a cause of most cervical cancer in the presence of the HPV infection. A meta-analysis of epidemiologic studies on multiple sexual partners as potential risk factors for cervical cancer showed that the risk is both stable in

the malignant and non-malignant with more than 4-7 sexual partners, suggesting that multiple sexual partners is a cervical cancer risk with or without HPV infection(Liu, Liu, Liu, Ye, & Chen, 2015).Also cooper et al stated that Lower socio-economic status, seem to be a factor for increased sexual activity which is proportionally related to educational level(Cooper et al., 2007).

2.4 Prevention of Cervical Cancer

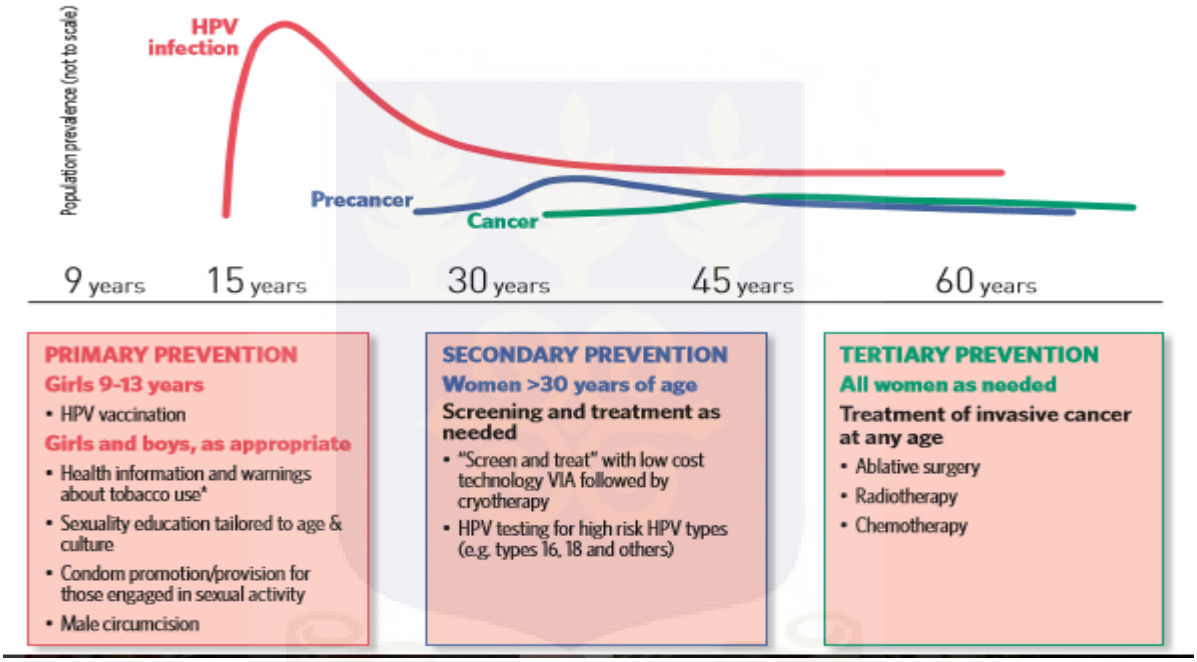

Figure 4: over view of programmatic interventions to prevent HPV and cervical cancer (Reproduced from WHO 2103)

2.4.1 Primary prevention

The prevention of cervical cancer is essentially based on the healthy lifestyles and prevention of HPV infection (abstinence from sexual intercourse, being faithful to the partner and consistent use of condom, increasing awareness among women who at risk and vaccination against HPV). The availability of effective HPV vaccinations is considered to be very important, and currently there are only two types of known vaccines;

the bivalent vaccine protects against the genotypes 16 and 18 and the quadrivalent vaccine protects against 6, 11, 16 and 18. These two vaccines have proven effective in the prevention of persistent infection caused by the two most important subtypes of HPV; 16 and 18. The quadrivalent vaccine also provides protection against other types of HPVs known to cause the majority of anogenital warts. Both types of vaccines have demostrated to be highly effective in preventing precancerous cervical lesion in women who have been vaccinated at a very early age before sexual debut.(Mahesa, 2012).The different HPV types and the difference in geography and certain risk factors ,renders the vaccine unable to cover all HPV infections,and though the aim is to immunize women who are not yet infected with the virus ,there is still the need to address women who already have oncogenic infection or pre-cervical lesions.

2.4.2 Secondary prevention

In secondary prevention, precancerous lesions may be detected through screening and early treatment which significantly reduces cancer related morbidities and mortalities. The reason for screening is that if the disease is detected early, any treatment required will be less extensive, more effective and more efficient (Mahesa, 2012). In developed countries where there are successful screening programs, death from cervical cancer seldom exceeds 5 per 100,000 women, while in Africa, especially in west Africa, a rate of 17 per 100,000 has been reported (kayumba, 2010). Precancerous lesions screening can be done through several methods including; Pap smear, visual inspection of the cervix with acetic acid or alternatively visual inspection with lugol's iodine and finally testing for HPV DNA.

2.4.2.1 Visual inspection with acetic acid (VIA)

Visual methods of screening include: Visual inspection with acetic acid , visual inspection with lugol's iodine, Visual inspection with low-level magnification, cervico-scopy aided visual inspection.

VIA is an alternate to Pap smear which is based on the naked eye examination of the cervix (squamo-columnar junction/transformation zone) with 3-5% acetic acid in the presence of adequate light source preferably halogen light. A test is said to be positive when it shows aceto-white lesions on the cervix. The aim of VIA is to detect aceto-white lesions which leads to the early diagnosis of cervical dysplasia and the early treatment before it reaches the invasive stage. VIA reduces the need for laboratories, specimen transportation and pathologist or cytologist. In the presence of adequate training and supervision, medical professionals of all cadres can effectively perform the procedure. Visual inspection with acetic acid has advantages over other screening methods in low-resource settings such as less equipment needed, improved follow-up, results are read immediately ,immediate treatment depending on the results, has larger coverage, and can be performed in remote or hard to reach areas(Balarabe, Musa, Chado, Garba, & and Musa, 2014). VIA has a higher sensitivity than Pap smear in detecting the high-grade lesions, but has a lower specificity. Screening can be performed by health professionals at any educational level or cadre. The true results of the test may be affected by several factors such as: differences in training and skills of the test providers, presence of an STI and lack of universal uniformity in the application are the gold standard for disease definition in these studies(Mahesa, 2012).Cross sectional studies for accuracy show that specificity to detect the precancerous cervical lesions ranges from 64%-98% with a median of 84% and the sensitivity ranges from 66%-96% with median of 82%.

A study was conducted on 2,400 women with use of acetic acid with naked eye and colposcopy showed that 98.9% of the cases were identified as normal whilst 98.4% had abnormalities with VIA (Ottaviano & Torre, 2016).In another study in Zimbabwe comparing VIA and cytology also showed that specificity of 64.1% to 90.6% and sensitivity of 76.7% to 44.3%.A Comparative study on VIA versus Pap smear in antenatal

women showed that out of the 113 patients screened 10 patients were VIA positive, among them 3 were found to be colposcopically positive. One patient found to be Pap smear positive, and subsequently found to be positive. In another study the detection rate of VIA was 2.65%, and Pap smear was 0.88%. In addition to the study the ratio of detection rate between VIA/PAP smear was 3.01(Thilagavathi & Geetha, 2016).A prospective comparative study of the effectiveness of pap smear against VIA and VILI on 210 patients showed, 16.27% were positive for Papsmear test, 213.87% were positive for VIA and 11.43% had positive VILI and finally 14.8% demonstrated features of CIN on colposcopy (Consul et al., 2012).A study in an Indian hospital comparing pap smear, VIA and colposcopy for VIA screening on 400 patients showed 96.7% sensitivity to VIA ,50% to pap smear and 100% to colposcopy whilst specificity was 36.6% to VIA, pap smear 97% and colposcopy 96.7%(Mustafa M , A.K Jindal, 2010). In Peru a study was conducted to assess VIA as a screening tool in a well-equipped health center on 1921 women and it showed that 132(6.9%) tested positive for VIA as compared with 80 (4.2%) for pap smear ,35 women had CIN1 (15 by pap smear and 20 by VIA), 13 had CIN 2 and 3 of which 84.6% were VIA positive and 38.5% had pap smear positive (Jeronimo et al., 2005).

468 women in Iran had both VIA and Pap smear test, 43 had VIA positive and 23 were Pap smear positive, sensitivity, specificity, PPV and NPV for the VIA were 66.7%, 55.1%, 18.6% and 91.5%, respectively whilst as for Pap smear test were 75%. 82.1%, 39.1% and 95.5%, respectively.Study showed that VIA had a higher sensitivity but lower predictive value (Keshavarzi et al., 2013). A study conducted in China by Belinson et al demonstrated that VIA had a sensitivity of 71% and a specificity of 74%(Belinson et al., 2001). However, for cervical cancer screening, sensitivity should be more important than specificity(Chumworathayi B, Limpaphayom K, 2006).

2.4.2.2 Cytology

Screening by Pap smear which involves the collection of the cells taken from the transformation zone and examined in the laboratory for abnormalities is the most common screen test, although its efficacy is not tested by the study trials, it is agreed that it has drastically reduced the incidence and mortality of cervical cancer in first world countries. Data from the International Agency on Research for Cancer on cancer mortality has shown that countries like US, Canada and UK have substantial reduction in mortalities related to cervical cancer as these countries implemented screening programs for the past 60years (Ibrahim, 2013).

The accuracy of the specificity of pap smear has been estimated using meta-analysis to range from 95%-99% and sensitivity of 60-90% in comparison to VIA and HPV testing(WHO 2002) .Pap smear test is usually recommended for the women between the ages of 25 and can be continued until the age of 60 and follow-up screening every three to five years which can reduce incidence by 80% (WHO, 2013).The Bethesda classification system, reports lesion as Low grade and high grade Squamous Intraepithelial Lesion. A further category of glandular cell abnormality named. In general terms, a cytological diagnosis of LSIL represents a histological diagnosis of CIN1 where as a cytological diagnosis of HSIL would represent CIN2 or CIN 3 lesions on histology.

CHAPTER THREE

METHOD

3.1Study design

The study was a descriptive cross-sectional study conducted at the Brikama District Hospital at the Anti-Retroviral Therapy (ART) clinic of the Hands on care medical centre in the Western Region of the Gambia from March to May 2017.Data was obtained through a pre –tested semi-structured questionnaire and after which patients were screened for cervical dysplasia (pre-malignant lesions) using Visual inspection with acetic acid.

3.2 Study Area

The study was done in The Gambia at Hands –on care medical centre in Brikama. The Republic of the Gambia is situated in West Africa and divided into two by the river Gambia which gets its sources from the Futa Jallon high lands in Guinea Conakry and empties itself in the Atlantic Ocean. The country has a total land area of 10,689 km sq. and a population of 1,882,450 with six administrative regions. Brikama is the capital of western Region of the Gambia and the second largest city in the country. It occupies a total land area of 1,764.25 km sq. and has a population of 699,704.Brikama is the most populous local government area in the country with a growth rate of 80% and divided into 9 districts. Majority of the people live in the rural areas and are mainly farmers. Located inland, in the South Bank, the main urban settlement is about 36km southwest of the Banjul capital and bounded by the river Gambia to its north, kanifing municipal council to the east, Mansakonko to the west and southern Senegal to the south.

Figure 5: Map of study area

3.3 Study site

The study was conducted at Hands on care medical centre.Hands on Care medical center is the country's leading ART site in the Gambia. Services provided include : sexual and reproductive health services, treatment, care and support for people living with HIV including Anti-Retroviral Therapy(ARVs),prevention and treatment of STIs including family planning, comprehensive palliative and a Home Based care, support for Orphans and Vulnerable Children, institution and community outreach including VCT and PMTC, and additional areas including health research, training and capacity building of healthcare workers .The center Has a total patient turnover of 60-80 patients per day , headed by a trained medical Doctor who is the medical Director and supported by well trained and qualified two medical doctors. Has a total staff population of 40 of which 3 are medical doctors, 15 are trained nurses ,5 lab technicians and the rest are support staff

and volunteers. It is housed within Brikama District hospital and they share some of the services such as laboratory, wards (medical, surgical and labor), theatre, public health unit, cervical cancer screening unit and etc. It cares for approximately 40 HIV women per clinic day and attends to all HIV confirmed cases both males and females including children and who are on or are not yet on anti-retroviral drugs. It runs 3 clinic days per week namely; Monday, Wednesday and Thursday. Eligibility meetings for ART commencement are usually held on Tuesdays and also have some trekking or outreach stations which are covered by the staff. The Brikama district hospital's gynea clinic has a VIA screening unit which provides both family planning services and VIA screening and cryotherapy services. It serves approximately 400 women per month for both family planning and cervical cancer screening services (VIA).

3.4 Study population

The study population is all HIV infected women from ≥18 years and ≤ 60 years who had been or were sexually active, and attending the ART clinic of hands on care within Brikama District Hospital. Women on their routine follow- up visit for HIV who met the criteria and have consented to participate in the study were screened for cervical cancer using conventional VIA.

3.5 Inclusion and exclusion criteria

3.5.1 Inclusion criteria

All HIV infected women of ≥18 and ≤ 60years, who have been attending the out-patient clinic (HOC) and have consented to the study.

3.5.2 Exclusion criteria

- Women with obvious or advanced cancer of cervix
- Pregnant and lactating mothers(<3months postpartum)
- Eligible case not willing to participate
- Eligible case with physical or mental impairment and cannot tolerate interview.
- History of Hysterectomy

3.6 Variables

3.6.1 Outcome variable

The dependent variable: VIA status

3.6.2 Independent variables

Socio-demographic factors	Reproductive factors	Behavioral factors	Clinical factors
• Age	• Age at first sex	• Life time sexual partners	• Duration of HIV diagnosis
• Education	• Age at first birth	• Tobacco use	• CD4 count
• Marital status	• Parity		• WHO clinical staging
• Marriage type	• Contraceptive use		• HAART use
• Occupation	• Contraceptive type		• HAART regimen
• Religion			

Table 2: O**perational definition of socio-demographic variables**

Variable	**Operational definition**	**Scale of measurement**	**Source of data**
Age	Age at last birthday in years	Continuous-discrete	interview
Educational level	Highest level of education attained	Categorical • No formal education • Primary • Secondary and above	interview
Marital status	Whether married ,single ,divorced or widowed	Categorical • Single • Married • Divorced • Widowed	interview
Type of marriage if ever married	Whether monogamous or polygamous	Categorical • Monogamous • polygamous	interview
Occupation	Employment status	Categorical • Unemployed • Formal • Informal/self employed	interview
Religion	Religious belief/faith	Categorical • Christian • Muslim • Other	interview

Table 3: Operation definition of behavioral characteristics

variable	Operational definition	Scale of measurement	Source of data
Number of life time sexual partners	Number of sexual partners	Continuous-discrete	interview
Ever used tobacco	Ever used tobacco	Categorical • Yes • No	interview

Table 4: Operational definition of reproductive characteristics

variable	Operational definition	Scale of measurement	Source of data
Age at first intercourse	Age at first sex in years	Continuous-discrete	interview
Age at first birth	Age at first delivery	Continuous – discrete	interview
parity	Number of children	Continuous-discrete	interview
Contraceptive use ever	Ever used contraceptives	Categorical • Yes • no	interview
Type of contraceptive	Type of contraceptive if ever used	Categorical • Pills • Depo/injectable • IUCD/Jadelle	interview

Table 5: Operational definition of clinical characteristics

variable	Operational definition	Scale of measurement	Source of data
Duration of diagnosis with HIV	When diagnosed with HIV in years	Continuous-discrete	Hospital records
CD4 baseline	CD4 baseline	Continuous-discrete	Hospital records
CD4 current	CD4 current	Continuous-discrete	Hospital records
WHO clinical staging	WHO clinical staging	Continuous –discrete	Hospital records
HAART use	HAART use	Categorical • Yes • No	Hospital records
HAART regimen	HAART regimen	Categorical • First line • second line	Hospital records
Previous screening	Previous cervical cancer screening	Categorical • Yes • No	interview

3.7 Sampling

3.7.1 Sample size determination

The cervical cytology abnormalities prevalence in HIV-infected women ranged between 12.5% to 38.3%. For the study the prevalence of the cervical dysplasia in HIV-positive women was taken as an average of 12.5% and 38.3% thus 25.4%. The formula used for this study was:

$$n = \frac{Z^2 * p(1-p)}{d^2}$$

$$n = \frac{Z^2 * p(1-p)}{d^2}$$

n=minimum sample size

Z = the critical value associated with the level of significance (1.96 for 95% level of confidence)

p=the prevalence of cervical dysplasia in HIV infected women at 25.4 %(0.254)

d=precision/reliability to determine p=5% (0.05)

$$n = \frac{1.96^2 * [0.254(1-0.254)]}{0.05^2}$$

$$\frac{0.98(0.75)}{0.0025}$$

Thus n=292(minimum sample)

Ten percentage of this number (30) is going to be added to take care of the attrition in the study population. This brought the total number of study participants to be recruited to 322.

3.7.2 Sampling method

A Systematic sampling is used to choose the study participants for the cross sectional study. The facility had a client base of 1440 clients for the period of study. Therefore the expected number of women for the cross sectional study was 1440.

The sampling interval (k) = 1440/ 322

$$\frac{1440}{322}$$

=4.47

=4

Amongst all the HIV infected women attending the clinic, after every routine clinical checkup, the first four names of the patients on the list were written on pieces of paper, put in a box, then the first name was randomly selected from the box and subsequently, every fourth woman was systematically selected on the list until the sample size was attained. If any one person does not meet the inclusion criteria, the subsequent one was selected.

3.7.3 Recruitment process

The data was collected within a period of three months .Prior to the study two research assistants were recruited based on;

- Being trained midwives
- Having knowledge and actively screening women on VIA.

Data was collected through an interview using a pretested modified structured questionnaire based on the objectives of the study and the research questions and also review of patient's medical records during the clinic days (Monday, Wednesday and Thursday). The questionnaire included both categorical and open ended questions about the socio-demographic, sexual, behavioural data while the viral load (CD4 count) on the baseline and current amount, HAART status and WHO stage were obtained from patient's medical records then subsequently , VIA results were obtained immediately after performing the test on patients.

3.8 Data collection technique.

Data collection was carried out in the ART clinic of the medical Centre. Patients already selected from their routine HIV clinic visit were escorted to a well prepared interview room ,equipped with an examination bed, adequate light source ,instrument tray, cotton swabs ,sterile vaginal speculums, surgical gloves and 5% acetic acid and there the study was explained to them including the VIA procedure and Informed consent signed .

3.8.1 Review of patient's records

Medical records of HIV positive women who consented to the study were reviewed for the following; WHO-Clinical staging, CD+4 count (baseline and current), HAART use and regimen and finally duration of HIV diagnosis.

3.8.2 Interview

An interviewer assisted questionnaire was administered face-to-face by the researcher or a research assistant in the interview room , the tool captured patient socio-demographics such as age, age at first coitus, marital status, marriage type, religion, educational level, occupation, parity, number of life sexual partners, contraceptive use and duration of HIV diagnosis.

3.8.3 Screening procedure

After interviewing the patient, the principal investigator performed the VIA procedure in which the patient was encouraged to relax and was asked to lie down on the examination bed, in a lithotomy position, with both feet place on metal stirrups to spread legs apart and also to flex the knees, buttocks were also positioned to the edge of the bed to enable easy examination and have a clear view of the vagina. Patients were asked to remove clothing covering from lower abdomen to mid-thigh. After proper positioning, with worn sterile surgical gloves, examination of vagina for any vaginal discharges was done, also

examined for any of the signs of excoriations, edema, vesicles, papules, sores, ulcerations, warts and swellings.In the presence of a good source of light focused in the vagina, a sterile disposable Cusco's speculum was inserted through the vagina to reach position and visualise the cervix. All secretions were gently wiped off with a clean sterile cotton swab and freshly prepared 5% acetic acid was gently applied on the visible cervix using an acetic acid soaked swab, after 3mins of application, and observation for the appearance of a white lesion on the cervix or the transformation zone close to the squamocolumnar junction and results were read immediately. Results were reported as either positive or negative depending on the findings and VIA positive were considered when there were a distinct, well-defined and densed acetowhite areas with regular or irregular margins, and cryotherapy was performed with oxygen to remove precancerous lesions and recommended for follow-up after the 3 months for clinical evaluation and later for rescreening. If a lesion was suspicious of invasive cervical cancer (clinical signs), women were referred to the Edward Francis small teaching hospital for colposcopy, biopsy and specialist review.

3.9 Data quality control

Training of research assistants was conducted on the objectives, interview techniques and data quality of the study.

Before data collection, 20 questionnaires were pre-tested in another ART centre which was aimed at helping the research assistants to be conversant with the data collection tool and also give an opportunity to make the necessary corrections or amendments. In addition based on the clinic days, the principal investigator collects and checks the completed forms and corrects errors that arose during the process, completeness and consistency

before data entry was done. To ensure quality, 10% of the negative VIA tests were repeated by a different trained midwife at another screening site.

3.10 Data processing and analysis

Data was entered, filtered and cleaned in excel and later imported to STATA version 13 for analysis. Questionnaire and responses were typed, entered and saved manually. Double entry verification of the questionnaires was done to ensure the validity of the entry. Graphical and tabular techniques included frequencies. Descriptive statistics,(mean, standard deviation, percentages and frequency distribution) were used to analyse the quantitative data to determine central tendency and proportion. VIA results were recorded as either positive or negative. Pearson chi square test was performed to determine the significant difference between VIA positive and categorical variables and presented as contingency table with p-values and the fisher's exact test was used to test for variables with less than 5 frequencies .Binary logistic regression was done to determine risk factors associated with cervical dysplasia and variables with a p-value of < 0.05 was then considered statistically significant .Variables which were statistically significant at the binary level were further regressed at the multiple logistic level .The findings were presented in tables of frequencies, percentages, crude odds ratio, adjusted odds ratio, 95% confidence interval and p-values.

3.11 Ethical considerations

The ethical clearance was obtained from the Research and Ethics review committee of the Gambia. An application for the ethical clearance from the school of medicine and allied health sciences research and publication committee (RePubliC) was done and also permission was also sought from the Hands on care Board and management. Written

informed consent was sought from each patient before administering the questionnaire. Permission letters and consent forms were available in English and explanation was done in the local language (Mandinka, Wollof, and Jola) suitable for the patient for comprehensive understanding, potential risks and benefits and assurance of confidentiality. Health talks were also done with poster/picture illustrations on every clinic day. Patients were given the opportunity to ask questions before signing consent and also to refuse or withdraw from the study at any point and their privacy was respected .Names of patients were not used, as the questionnaires were coded with their ART numbers and all information was treated as confidential. The collected data was only accessible to those involved in this research and all data was entered in the computer and the electronic spread sheet was saved with a password.

3.11.1 Informed consent

Even though a routine counseling is in place for HIV and AIDS patients, a pretest voluntary counseling was done, permission and consent was sought from the patients and when granted a questionnaire was administered to each participant and VIA was performed. The trained research assistants translated the questionnaires into local languages to the best of the understanding of a patient in the presence of an independent witness where the recruited patient cannot read and write.

3.11.2 Confidentiality and anonymity

Screening and ART numbers were used for participants as identity numbers since names were not used on the questionnaires. The participants were assured of the confidentiality of the provided information during the process of obtaining a consent and privacy was maintained throughout and personal information such as home address, contact detail and other confidential information were not required. Completed questionnaires and VIA

results were captured, entered in the computer and the electronic spread sheet was saved with a password.

3.12 Training of interviewers/pre-testing of tools

Training of research assistants was conducted by the principal investigator on the collection technique, the objectives of the study and how to conduct interviewer administered questionnaire. Refresher training on performing VIA was done for two weeks after which, questionnaires were pre-tested in order to determine applicability and appropriate corrections were made for the study. An explanation of the purpose of the study and its ultimate benefits to the patients were stressed upon and emphasis were made that participation was voluntary after which an informed consent was obtained in a language clear to the patient either English of any of the local languages.

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CHAPTER FOUR

RESULTS

A total number of 322 HIV infected women were screened using VIA at Hands on care medical center in Brikama from March to May 2017 and 22% (70/322) were positive for the VIA test whilst 78 %(252/322) were negative.

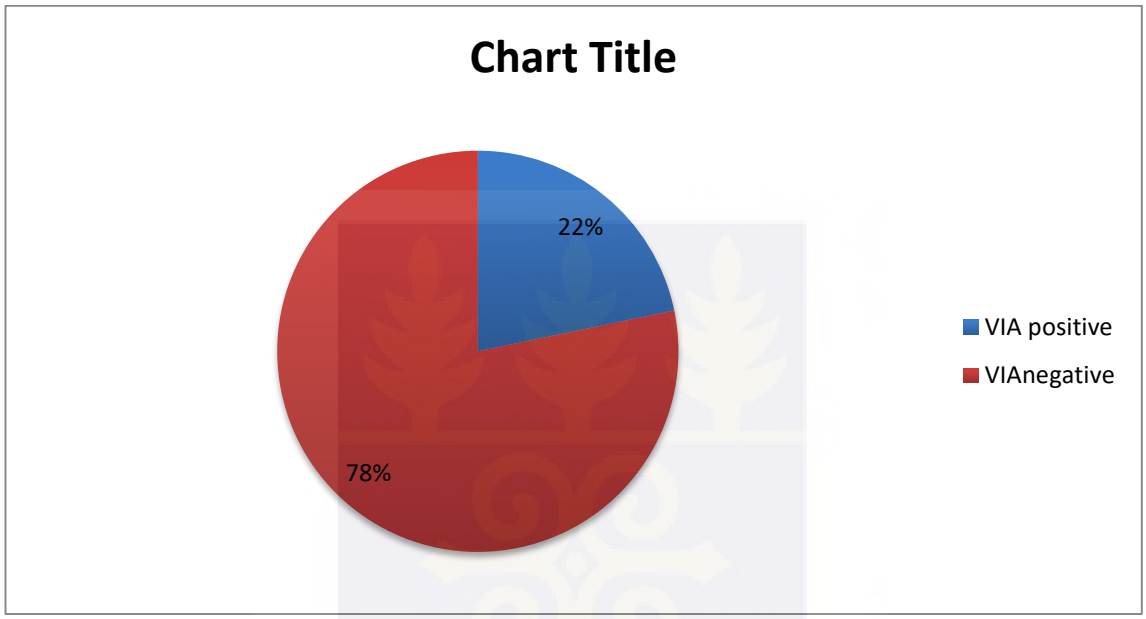

Figure 6: Prevalence of acetowhite lesions with 5% acetic acid

4.1 Descriptive statistics

4.1.1 The Socio- Demographic characteristics

Table 6 (below) shows the socio-demographic characteristics and VIA status of the HIV women screened for the cervical cancer. The mean age ± SD(years) of the VIA positive women was 37.3±8.0 and VIA negative was 39±7.5 and the majority of the women were between the ages of 36-49 years .The difference in age was highly significant(χ^2 =10.0;p-value= 0.01).Women with tertiary educational levels formed the majority 61%(198/322)and there was no significant association between the different educational

level and the risk of developing cervical dysplasia(χ^2=1;p-value=0.6).Married women formed the majority,45% (146/322) of the women screened and marital status was not significantly associated with developing cervical dysplasia(χ^2=1.9;p-value= 0.6).Concerning the religious background, most of the 94%(303/322) of the women belonged to the Muslim faith and polygamy was practiced by 74% (234/318) which is typical of the community where the study was conducted and there was no significant association between the different religious faiths, marital practices and the risk of developing cervical dysplasia .(χ^2 =1.5;p-value= 0.2), (χ^2 =1.8;p-value= 0.4)respectively.

The odds of developing cervical dysplasia or pre-malignant lesions was 2.7times more in the women between the ages of 26-35years as compared to women between 18-25 years (cOR=2.7;95%CI 0.3-23.6;P-value0.02)(Ref:18-25),findings showed that age was significantly associated with the development of cervical dysplasia. The results showed educational status of women was not associated significantly with the development of dysplasia (P≥0.05) and the odds of developing dysplasia in those with primary education is 0.8 times lesser than those with no formal education(cOR=0.8;95%CI 0.3-0.9;p-value 0.6)(Table 6). Compared to single women, divorced women have 0.7 times lesser odds to develop cervical dysplasia than single/unmarried women (cOR=0.7; 0.9: 95%CI=0.32-1.61;p-value0.7). Compared to women in monogamous relationships, women in polygamous relationships have 1.1 times higher odds to develop dysplasia (cOR=1.1; 95%CI 0.6-2.1;p-value0.8).The odds of developing dysplasia in women in the informal employment sector are 1.1times higher than other women in the formal sector (cOR=1.1; 95%CI 0.6-1.0;p-value0.9). Being a Muslim, the odds of developing dysplasia was 2.5times more than non-Muslims, but no association of significance was found (cOR2.5; 95%CI=0.6-10.9; p-value0.2).

Table 6: Socio-demographic characteristics of HIV positive women screened for VIA

variable	VIA positive N (%)	VIA Negative N (%)	cOR	95% CI	p-value
socio-demographic					
Age					**0.02*+**
Age(mean)	37.3±8.0	39.0±7.5			
18-25	1(1.4)	6(2.3)	1		
26-35	36(51.4)	79(31.3)	2.7	(0.3-23.6)	0.4
36-49	26(37.1)	140(55.6)	1.1	(0.1-9.6)	0.9
≥50	7(10)	27(10.7)	1.6	(0.2-15.1)	0.7
Education					**0.6**
No formal	14(20)	52(20.6)	1		
primary	10(14.3)	48(19.1)	0.8	(0.3-1.9)	0.6
≥secondary	46(65.7)	152(60.3)	1.1	(0.6-2.2)	0.7
Marital status					**0.7+**
single	0(0)	4(1.6)	1		
married	31(44.3)	115(45.6)	0.8	(0.4-1.5)	0.5
divorced	10(14.3)	43(17.1)	0.7	(0.3-1.6)	0.4
widowed	29(41.4)	90(35.7)	1		
Marriage type					**0.8**
monogamy	17(30.4)	67(32.5)	1		
polygamy	39(69.4)	139(67.5)	1.1	(0.6-2.1)	0.8
Employment					**0.9+**
unemployed	21(30)	81(32.1)	1		
formal	3(4.3)	12(4.8)	1	(0.2-3.7)	1
informal	46(65.7)	159(63.1)	1.1	(0.6-1.0)	0.7
Religion					**0.2+**
Christian	2(2.9)	17(6.8)	1		
Muslim	68(97.1)	235(93.3)	2.5	(0.6-10.9)	1.2

*(p-value≤0.05)

+ (fisher's exact test)

4.1.2 Reproductive risk factors for cervical cancer

Out of the 322 women who were screened, the mean age and SD (years) of first sexual intercourse was 16.9±2.9 for VIA positive, whilst VIA negative was 17.1±3.0 and half of

them at least 51% (165/322) had their first sexual intercourse between the 16 and 20 years of age and it was significantly associated with the risk of developing cervical dysplasia. (χ^2 =6.8;p-value=0.03) (Table 7). Similarly, the mean age and SD (years) at first birth was 18.5±6 for positive VIA whilst 18.4±4.1 for negative VIAs and 60% (192/322) of the women were between the ages of 16-20 years and was also associated with the risk of developing cervical dysplasia(χ^2 =11.3;p-value= 0.004).

Moreover, 95% (307/322) had children and of which 91% (294/322) have between one and three number of children and its association was found to be statistically significant with the risk of developing dysplasia (χ^2 =9.3; p-value= 0.01.More than half of the women 55% (177/322) had ever used contraceptives and of which 59%(105/177) used it for less than five years. Contraception was not associated with developing cervical dysplasia (Table7).

The study found that as compared to women who had their first sex at < 16 years, those who had their first sexual intercourse at more than 21 years of age had a 0.1 lesser odds of developing cervical dysplasia than women who had it at less than 16 years and the association was statistically significant (cOR=0.1; 95% CI 0.02-1.2; p-value 0.01). Also similarly to women who had their first deliveries at the same age were 0.3 times less likely to develop dysplasia than those younger than 16 years and the association was statistically significant (cOR;95% CI 0.1-1.0;p-value 0.01).Women who had no children were found to be protected from the disease with an odds ratio 0.5,whilst having four or more children as compared to nulliparous women was 3.8 times higher odds to develop cervical dysplasia and was found to be statistically significant(cOR;95%CI 0.7-19.7;p-value 0.02) .Further more women who have never used contraceptives were neither at risk nor protected from dysplasia (cOR;1;95%CI 0.6-1.6;p-value 0.9) whilst use of contraceptives for more than 5 years gives an odds ratio of 0.8times less likely to develop the dysplasia.

Table 7: Reproductive characteristics of HIV positive women screened for VIA

variable	VIA positive N (%)	VIA Negative N (%)	cOR	95%CI	P-value
Age at first intercourse(years)					**0.01*+**
Age(mean)	16.9±2.9	17.1±3.0			
<16	27(38.6)	102(40.5)	1		
16-20	42(60)	123(48.8)	1.3	(0.7-2.2)	0.4
≥21	1(1.43)	27(10.7)	0.1	(0.02-1.2)	0.06
Age at first birth(years)					**0.01*+**
Age(mean)	18.5±5.8	18.4±4.1			
<16	23(32.9)	39(15.5)	1		
16-20	37(52.9)	155(61.5)	0.4	(0.2-0.8)	0.01
≥21	10(14.3)	58(23.0)	0.3	(0.1-1.0)	0.04
Children					**0.3**
yes	65(92.9)	242(96.0	1		
no	5(7.1)	10(4.0)	0.5	(0.2-1.6)	0.3
Parity					**0.02*+**
None	3(4.3)	10(4.0)	1		
1-3	59(84.3)	235(93.3)	0.8	(0.2-3.1)	0.8
≥4	8(11.4)	7(2.8)	3.8	(0.7-19.7)	0.1
Ever used contraceptive					**0.9**
yes	39(55.7)	138(54.8)	1		
no	31(44.3)	114(45.2)	1	(0.6-1.6)	0.9
Contraceptive type					**0.4+**
pill	14(35.9)	42(30.9)	1		
Depo/injectable	22(56.4)	72(52.9)	0.9	(0.4-2.0)	0.8
Implanon/Jadelle	3(7.7)	22(16.2)	0.4	(0.1-1.6)	0.2
contraceptive length(years)					**0.5**
<5	25(64.1)	80(58.4)	1		
≥5	14(35.9)	57(41.6)	0.8	(0.4-1.6)	0.5

*Significant (p≤0.05)

+(fisher's exact test)

Out of the 177 who have ever used contraceptives, the most widely used contraceptive method for both VIA positives and negatives was the Depo-Provera (injectable) 56.4%, and 52.9% respectively.

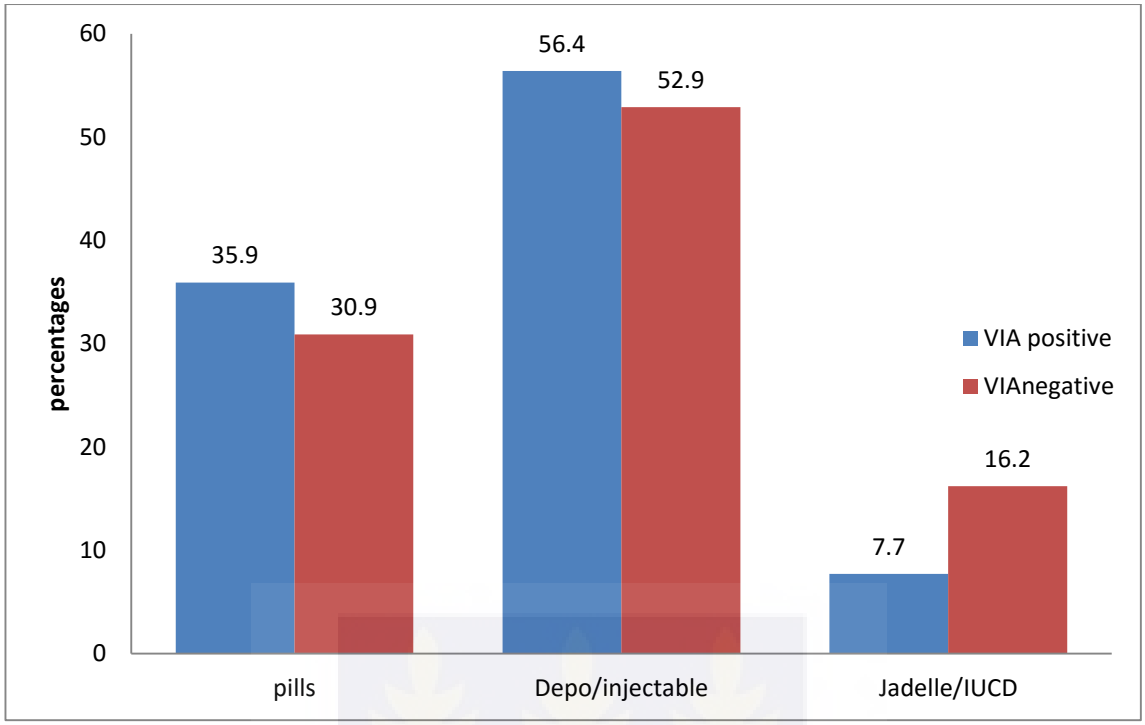

Figure 7: Graph of various contraception used by the HIV infected women

4.1.3 Clinical risk factors

More than half of the participants 53% (172/322) were diagnosed with HIV more than 5 years ago and of which had a CD4 baseline count of below 200/mm^3 as 35% (112/322) and 81% (262/322) had current CD4 count above 200mm^3 both were not statistically significant(Table 8).89% (286/322) of the women were in WHO stage II and more than 90% (303/322) were boarded on highly active antiretroviral treatment (HAART) of which almost half, 52% (159/303) were taking the second line of HAART regimen.

The odds of developing cervical dysplasia is 1.1times higher in women who were diagnosed with HIV less than 5years (cOR=1.1;95 %CI 0.4-3.1;p-value 0.8).The odds of developing dysplasia with a baseline CD+4 count of more than 200 was 1.7times higher and also a 0.9 lesser with a current CD4 count and the study showed that CD4 count was not significantly associated with the disease.(cOR:1.7;CI 0.9-3.1;p-value0.06) and (cOR:0.9;CI 0.5-1.7;p-value 0.7) respectively. Compared to WHO stage I, the odds of

developing dysplasia in stage II was 1.4 times higher than in stage I (cOR;95%CI=0.4-4.2).Women who are not on HAART have an odds of 0.4times less to develop the disease than women who are (cOR0.4;95%CI 0.2-1.2;p-value 0.1) and those on second line HAART regimen have the odds of 0.7 times less to develop the disease.

Table 8: Clinical characteristics of HIV+ women screened for VIA

variable	VIA positive N (%)	VIA negative N (%)	cOR	(95%CI)	p-value
HIV diagnosis duration(years)		**0.8**			
<1	5(7.1)	18(7.1)	1		
1-5	40(57.1)	132(52.4)	1.1	(0.4-3.1)	0.9
>5	25(35.7)	102(40.5)	0.9	(0.3-2.6)	0.8
CD4 count					
Baseline					**0.06**
<200	18(25.7)	94(37.3)	1		
>200	52(74.3)	158(62.7)	1.7	(0.9-3.1)	0.07
Current					**0.7**
<200	14(20)	46(18.3)	1		
>200	56(80)	206(81.8)	0.9	(0.5-1.7)	0.7
WHO clinical staging					**0.9**[+]
1	4(5.7)	19(7.5)	1		
2	64(91.4)	222(88.1)	1.4	(0.4-4.2)	0.6
3	2(2.9)	7(2.8)	1.3	(0.2-9.1)	0.7
4	0(0)	4(1.6)	1		
HAART USE					**0.1**
Yes	63(90)	240(95.2)	1		
No	7(10)	12(4.8)	0.4	(0.2-1.2)	0.1
HAART Regimen					**0.2**
First	35(55.6)	109(45.4)	1		
second	28(44.4)	131(54.6)	0.7	(0.3-1.2)	0.2
Previous cervical screening					
Yes	0(0)	6(2.4)			
No	70(100)	246(97.6)			

4.1.4 Behavioral Risk factor

Majority of the women 41%(133/322) had only one life time sexual partner and more than 95%of the women had never been screened before for cervical cancer and both factors were not associated with cervical dysplasia.

The odds of developing dysplasia in women with two to three life time sexual partners was 1.2 times higher than those with only one partner and was not significant(cOR=1.2;95%CI 0.7-2.3;p-value 0.6) and those who have never used tobacco had an odds of 0.4 lesser to develop dysplasia(cOR0.4;95%CI=0.1-3.1;p-value 0.3).

Table 9: Behavioral characteristics of HIV positive women screened for VIA

variable	**VIA positive N (%)**	VIA negative N (%)	cOR	95%CI	P-value
partners					**0.6**$^{+}$
1	27(48.2)	106(51.7)			
2-3	27(48.2)	86(42)	1.2	(0.7-2.3)	0.5
≥4	2(3.6)	13(6.3)	0.6	(0.1-2.8)	0.5
Ever used tobacco					**0.3**$^{+}$
Yes	1(1.4)	9(3.6)	1		
No	69(98.6)	243(96.4)	0.4	(0.05-3.1)	0.4

4.2 Multiple logistic regressions of risk factors

Multiple logistic regressions was conducted on all the statistically significant risk factors at the binary logistic level at p-value of ≤ 0.05 and at 95% confidence interval for the risk factors such as the age, age at first sex, age at the first delivery and the parity. Of these four which were significant at the binary level, are still significant at the multiple logistic level (Table 10).

Table 10: Multiple logistic regressions of factors associated with cervical dysplasia

variable	VIA positive	VIA negative	cOR	95%CI	P-value	aOR	95%CI	P-value
Age(years)					**0.02**			**0.02***
18-25	1(1.4)	6(2.3)	1			1		
26-35	36(51.4)	79(31.3)	2.7	(0.3-23.6)	0.4	3.0	(0.4-26.3)	
36-49	26(37.1)	140(55.6)	1.1	(0.1-9.6)	0.9	1.3	(0.1-11.0)	
≥50	7(10)	27(10.7)	1.6	(0.2-15.1)	0.7	1.8	(0.2-18.2)	
Age at first intercourse(years)								**0.001***
<16	27(38.6)	102(40.5)	1		**0.01**	1		
16-20	42(60)	123(48.8)	1.3	(0.7-2.2)	0.4	2.7	(1.2-6.1)	
≥21	1(1.43)	27(10.7)	0.1	(0.02-1.2)	0.06	0.3	(0.03-2.8)	
Age at first birth(years)					**0.01**			**0.002***
<16	23(32.9)	39(15.5)	1			1		
16-20	37(52.9)	155(61.5)	0.4	(0.2-0.8)	0.01	0.2	(0.1-0.5)	
≥21	10(14.3)	58(23.0)	0.3	(0.1-1.0)	0.04	0.3	(0.1-0.6)	
Parity					**0.02**			**0.002***
nulliparous	3(4.3)	10(4.0)	1			1		
1-3	59(84.3)	235(93.3)	0.8	(0.2-3.1)	0.8	2.6	(0.5-13.2)	
≥4	8(11.4)	7(2.8)	3.8	(0.7-19.7)	0.1	16.6	(2.2-124.4)	

*significant (p-value≤0.05)

CHAPTER FIVE

DISCUSSION

The study has demonstrated that factors independently and significantly associated with cervical dysplasia include: age of woman, the age at first sex, the age at first birth and parity. Moreover, the study demonstrated a high proportion of the cervical dysplasia in the HIV infected women who were screened.

5.1 Proportion of "cervical dysplasia in HIV infected women"

In the study 70 out of the 322(22%) HIV infected women did have cervical dysplasia or premalignant lesions (VIA positive).This finding is similar to a previous study conducted in southern Ethiopia on precancerous cervical lesions prevalence in HIV infected women which showed a prevalence of 22.1% (Gedefaw et al., 2013).Another similar study which was conducted in Kenya for resource limited settings showed a prevalence of 26.7% (Memiah et al., 2012). L. kafuriki et al(mwanza-Tanzania) also conducted a study which also demonstrated a prevalence of 26.8% on acetowhite lesions(Kafuruki et al., 2013).However other studies have reported lower prevalence of the cervical dysplasia in the HIV infected women within sub-Saharan Africa. In Nigeria(Abuja teaching hospital and national hospital) a study conducted on 2510 HIV infected women showed a prevalence of 6% (Akarolo-Anthony et al., 2013) and also in cote d'Ivoire a prevalence of "9.0% (95% CI 8.0-10.0) in the 2,998 HIV"-infected women screened with VIA(Horo et al., 2012) was reported .In Rwanda a total of 1002 HIV infected women were screened on VIA and results showed a prevalence of 5.9%(Makuza et al., 2015).Another study conducted in Botswana also showed a prevalence of 11.6%(Ramogola-Masire et al., 2012).A northern Thailand a study showed a VIA test-positive proportion of 13.3% in the nearly 6,000 women(Chumworathayi B, Limpaphayom K, 2006) and recently in Fuji

recorded a rate of 8-15% prevalence rate (Fong et al., 2014).Higher prevalence have also been reported in other studies ;in south Africa a prevalence of 66.3 %, Uganda reported 73%, and Zambia also reported 76% (Moodley et al., 2009),(Veldhuijzen et al., 2011) and(Walker, Kambugu, & Whalen, 2010) respectively. The difference between this current study and those of other researchers may be Associated with the difference in geography, sample sizes and possibly the different stages of HIV infection during screening.

Test of proportions was conducted in three different studies, a study conducted in Cote d'Ivoire on cervical cancer screening (VIA) showed a very significant difference in the proportion between the two studies with a p-value (<0.0001;CI:0.2-0.3).In addition another study conducted in Rwanda on the prevalence and risk factors of cervical and pre cancer lesions on HIV infected women also showed a significant difference in the proportion of cervical dysplasia with a p-value (<0.0001;CI:0.2-0.3).Also a study conducted in Nigeria on cervical dysplasia in HIV infected women has shown some statistically significant difference in the proportion with a p-value(0.004;CI:0.2-0.3).The significant difference could be attributed to the difference in the sample size and immunity level of the participants.

5.2 Risk Factors Associated with Cervical Dysplasia

The mean age of the HIV infected women who were screened in this study was 38.6 years with a standard deviation of 8 and the majority of the women fifty-two percent (166/322) were between 36 and 49 years of age. This finding showed similarities with cervical diagnosis in the general population. A similar study in Swaziland show age of <30 years as a significant risk factor for cervical lesions (OR=2.395%CI;O.9-6.1)(Jolly et al., 2017).Another similar study conducted in rural china on epidemiological investigation and

risk factors for cervical cancer lesions has shown age to be significant (OR=0.13;95%CI;0.03-0.6;p-value0.007)(Wang & Cui, 2016). In addition a study conducted by Braaten and Laufer concluded that diagnosis of CIN usually occurs between 25-30 years of age(Braaten & Laufer, 2008).Invasive cervical cancer usually peaks between 50 -60 years in general ,and the current finding is about a decade or two younger demosntrating that HIV usually shortens the rapid progression or transformation from pre-cancerous to cancerous stage.

Education and socioeconomic status dictates the living standard of a person .In this current study there was no significant finding between dysplasia and educational level. A study on HIV and pregnant women in Rwanda has demonstrated that education was not significantly associated with education level(Leroy et al., 1999).

Marital status was found to be not significant in this study as compared to other studies which had shown that the HPV is usually transmitted through sexual intercourse. Similar to this study, a study conducted in Swaziland has demonstrated no significant association as a risk factor (Jolly et al., 2017). A study conducted in India has shown that married women are more at a risk of developing cervical cancer than the single/unmarried women(Fotra, Gupta, & Gupta, 2014).In addition another study conducted in Abidjan on HPV and HIV infected women has also shown a significant association(p-value;0.01) between being married and harboring(A Jaquet et al., 2012) the oncogenic HPV.A similar study conducted in Tanzania in HIV infected women has demonstrated an insignificant association between marital status and risk of developing dysplasia(Kafuruki et al., 2013).Another study in Rwanda on the prevalence of the cervical pre-cancer and cancer lesions and risk factors has shown a significant association with being unmarried (P=0.04;OR=2.6 ;95%CI= 1.05-6.69)(Makuza et al., 2015).

A characteristic such as polygamous practices has shown to increase the risk of dysplasia. The increased number of partners increases the HPV transmission and therefore eventually increases the risk of developing dysplasia. In this current study, both polygamy and religion were not statistically significant, but there was an increase risk in developing dysplasia. In The Gambia, polygamy is a common practice and typical for a Muslim country were the data was collected. Contrary to the study a research conducted in Mali on risk factors of invasive cervical cancer has shown a significant association with polygamy (OR = 5.3, 95% CI : 1.3–21.3)(S. et al., 2002).

First sexual intercourse between the ages of 16 and 20 years has repeatedly been mentioned as a risk factor to cervical dysplasia or premalignant lesions. In this study sexual intercourse between the ages of 16 and 20 years was associated with the development of cervical dysplasia and was statistically significant. The findings were similar to other studies conducted such as a study in Rwanda which showed that sexual activity <20years (OR=1.75; 95% CI1.01, 3.03) (Makuza et al., 2015). A pooled analysis from eight developing countries demonstrated odds ratio of 1.80 (95% CI: 1.50–2.39) among women with 17–20 years of age and 2.31 (95% CI: 1.85–2.87) ≤16 years(Herrero et al., 2009).Another study among rural Indian women showed a significant association between cervical cancer and early age at first intercourse(OR :3.0, 95% CI : 1.1–8.0,p-value:0.03)(Biswas, Manna, Maiti, & Sengupta, 1997).Though other studies have also found varying results such as a similar study conducted in Tanzania on HIV infected women showed early sexual debut could be associated with development of CIN but it was not statistically significant(Kafuruki et al., 2013).Also another study in Tanzania showed that early sexual debut was not found to be directly associated with CIN(Kapiga, Msamanga, Spiegelman, & Mwakyoma, 1999),(Obure et al., 2009).The difference could be justified by a difference in the estimated sample size and geographical location.

Commencement of early sexual intercourse increases the likelihood of giving birth at an early age, multiple life time sexual partners and high parity. Early age at first birth was statistically significantly associated with cervical dysplasia. Studies previously conducted have also shown similar association .A case control study in eight third world countries showed a more than twice increased risk among those who report age at first birth at ≤ 16 years than ≥ 21 years(OR:4.10; 95% CI:3.36-4.9;p-value;<0.001)(Herrero et al., 2009).In another study the Rwanda <20 years old at the first pregnancy (OR:2.10; 95% CI:1.20, 3.67 p-value:0.009)(Makuza et al., 2015).

Most cervical cancer studies have been associated with parity as the most common reproductive risk factor in both first and third world countries, the mechanism in which high parity is an associated risk factor may be due to repeated trauma or tissue damage with superimposed hormonal changes causing cellular alteration during delivery or child birth.In this study increased parity was found to be statistically significantly (aOR:16.6;95%CI:2.2-124.4;pvalue:0.02). A study conducted in cote d ' Ivorie ,on risk factors of CIN on HIV infected women on ART showed that increased parity was highly statistically significant(p-value:0.004) (Antoine Jaquet et al., 2014).Another similar study conducted in Rwanda on pre-cancer and cancer risk factors in the HIV infected women showed an odds ratio of 8.7 times more in HIV infected women (OR =8.7; CI 2.3-32.4)(Anastos et al., 2010).A multicentric case control study of unknown HIV status showed 3·8 higher risk of developing the squamous cell cancer in women with seven or more pregnancies(OR=3.8;95%CI 2·7–5·5)(Muñoz et al.,2002).Also a hospital case–control study showed parity was significantly associated with cervical cancer(X^2 9.1;p-value:0.02)(Reis, 2011) .In addition a study conducted among Mozambican women has shown a significant association with increasing parity with a higher risk of 4times in women with five or more deliveries (OR:4.0;CI 2.03-5.44;p-value:0.00)(Rostad, Schei, &

Costa, 2003).Another study in Uganda showed that increased linearly with the number of pregnancies with 10 and above increases the risk of cervical cancer (X^2; P<0.0001) (Newton et al., 2007).Contrary to this study other studies have found different results. A study in Rwanda showed that increasing parity of five or more was rather a protective risk factor to precancerous lesions(Makuza et al., 2015).In addition a prevalence study of cervical squamous intraepithelial lesions in northern Tanzania showed no significant association between development of cervical SIL and parity(X^2 *:2.1;*p-value:0.545)(Obure et al., 2009). A case control(hospital based) study in Turkey has also shown a statistical significant association with increased parity (X^2:9.1 p-value 0.002)(Reis, 2011)

Contraceptive use is a risk factor for cervical dysplasia. A retrospective study conducted in Morocco by A.maamri et al has demonstrated an association between contraceptives and cervical cancer in women using injectable and pills to be 8% and 5% respectively(Maamri et al., 2012). A study conducted in Egypt showed an increased risk of use of oral contraceptives(OR; 4.93 95%CI;1.16-44.15) and duration of >5 years as a risk factor(OR:2.86; 95%CI :1.62-5.07)(El-Moselhy EA, 2016).In addition a case control study conducted in Dar es salaam in Tanzania showed a significant association with factors associated with cervical cancer(OR:1.19;95%CI:1.13–3.19;p-value:0.014)(Rweyemamu & MUHAS).Another study among Mozambican women showed a very significant association as a risk factor(Rostad et al., 2003). In addition a study conducted in Tanzania showed an increased risk of dysplasia (OR:1.01 95%CI:0.56-1.81;p-value:0.1)(Kafuruki et al., 2013).Contrary to the previous studies mentioned earlier in this study, we found no significant association in contraceptive use .Our findings agree with a similar study in Abidjan ,Cote d'Ivoire on risk factors of CIN which has shown no significant association with contraceptive use (Antoine Jaquet et al., 2014).Another similar study conducted in Rwanda has shown a similar result of no association with

contraceptive use (Makuza et al., 2015).In addition a study conducted in Nigeria on HIV infected women has also shown no significant association with contraceptive use and type of contraceptive(Ononogbu et al, 2013).Another study conducted in rural China on epidemiological investigation of risk factors of cervical cancer showed that contraceptive use is not associated with cervical cancer (OR:1.1;95%CI 0.4-2,844;p-value:0.9)(Wang & Cui, 2016).Another cervical cancer screening program conducted in Beijing on women has shown that use of contraceptives and its types was not significantly associated as a risk factor(Tao et al., 2014).

In this study the duration of diagnosis with HIV was not significantly associated with dysplasia. A study conducted in Tanzania on HIV positive women at Bugando Medical Centre,(Kafuruki et al., 2013)showed that the duration of diagnosis with HIV was not significant and also in another study conducted in Nairobi among prostitutes has a different finding, showing the likelihood of harboring high risk HPV which could lead to cervical dysplasia was among those diagnosed with HIV for more than two years(kreiss et al 1992).

Previous studies have shown associations between cervical dysplasia and the CD+4 count among the HIV infected women and a CD+4 count of < 200 cells/mm^3 is a precursor for having or developing dysplasia. A study conducted on cervical intraepithelial neoplasm risk factors on HIV infected women in Cote d' Ivoire showed an association between CIN and a CD4 count of <350cells/mm^3(Antoine Jaquet et al., 2014).Another study in Nigeria has shown that a low CDA count(<200cell/mm^3) was significantly associated with dysplasia(p-value:0.04)(Agaba, Thacher, Ekwempu, & Idoko, 2009).In addition a retrospective study on cervical in HIV infected women showed a significant association between CD4 count and cervical dysplasia and an increased risk(OR=24;95%CI:3.1–186.2;p-value<0.005)(Davis, Chakraborty, Flowers, & Mosunjac, 2001).

A study conducted in Kenya on risk factors and prevalence associated with precancerous lesions has shown an increased risk on women whose CD4 count was less than 200mm/^{3} with an odds of 1.6times more likely to develop dysplasia(Memiah et al., 2012).In another study in Tanzania among HIV-1 seropositive women, the risk of developing SIL in the women with CD+4 count <200mm^3 was 6times higher (OR :6.15, 95% CI:1.19-41.37).Another study in Abuja, Nigeria has demonstrated a strong statistical significant association between cervical pre-cancer lesion and CD+4 count of 650 per mm3 or more been a protective factor(RR=0.3,95%CI=0.2–0.6;p-value:0.0001)(Ononogbu et al., 2013).Contrary to the previous studies mentioned earlier ,this study has not shown any significant association between dysplasia and CD4 count(baseline and current).In support of this, a similar study conducted in southern Ethiopia has also shown a similar result of no significant association with CD4 count (Gedefaw et al., 2013).Another study in Rwanda also has a similar finding of no association with CD4 count(p-value:0.76)(Anastos et al., 2010).

In this study, the WHO clinical staging was not statistically significant, however a similar study in Nigeria has also had similar findings of an insignificant association with pre-cancerous lesions ,though the trend of increased risk progressively increased with increased stage(Ononogbu et al., 2013).Another study in Côte d'Ivoire had also shown an insignificant association between clinical staging and cervical intraepithelial lesions(p-value:0.94)(Antoine Jaquet et al., 2014).

Both initiation of HAART use and HAART regimen were not significantly associated with dysplasia. Use of HAART was found to be protective in this study. A study in Nigeria showed no significant association between HAART regimen and dysplasia (Ononogbu et al., 2013).Also another study in cote d' Ivoire showed no significant association with HAART use(Antoine Jaquet et al., 2014).

Having multiple sexual partners increases the risk of the HPV infection, and this, leads to the development of pre-malignant and cancer lesions. In this study 35% (113/322) of the women had 2-3 life time sexual partners which reported lower percentages as compared to other studies within the sub-Saharan region though it was not significant and in addition a study in Nigeria also showed 96% of the participants had between one and two life time sexual partners (Uzoma Ononogbu et al 2013).Another study in Côte d'Ivoire showed 56% of the participants had more than 5 lifetime sexual partners whilst in Zambia, a study reported that about eighty-five percent of the participants reported between one and five life time sexual partners(Groesbeck P. Parham et al, 2009).A similar study conducted in Ethiopia demonstrated that those with one lifetime sexual partner were 67% lesser to develop the precancerous lesion than those with more than one(Gedefaw et al., 2013).The difference in the prevalence can be due to large numbers used in their studies or limitations of self-reported sexual practices.

Use of tobacco has been known to cause cervical cancer in the presence of oncogenic human papilloma virus type. Nicotine and tobacco specific carcinogens are thought to directly produce some mitogenic effects leading to damage in the DNA of the cervical cells and also may affect the host's immune response against the virus. In this present study, the association of cervical dysplasia in the HIV infected women and those who have ever used tobacco were not significant. A study conducted in US on HIV infected women for cervical dysplasia has shown a similar finding of no statistically significant association between smoking and dysplasia(Davis et al., 2001).A similar study conducted in southern Ethiopia on precancerous cervical lesions prevalence in HIV infected women has shown no significant association with smoking(Gedefaw et al., 2013) .Another case control study conducted in côte d' Ivoire on HIV infected women has no significant association with tobacco use(p-value:0.15)(Horo et al., 2012).A study conducted in Swaziland on cervical

lesions prevalence and risk factors on HIV infected and uninfected women has demonstrated an insignificant association with smoking (p-value: 0.37) (Jolly et al., 2017). In addition another similar study conducted in Tanzania on the prevalence and predictors of CIN in the HIV women has also shown no significant association between exposure to cigarette and cervical intraepithelial neoplasia(Kafuruki et al., 2013).Contrary to this study , a study conducted in Henan province in rural China demonstrated an association between smoking and cervical lesions (OR=6.8;95%CI:0.6-44.6;p-value:0.030)(Wang & Cui, 2016).Another study in Canada on HIV and HAART evaluation on HPV and cervical cytopathologic findings on both HIV infected and uninfected women has shown a significant association with smoking(p-value<0.01) (Blitz et al., 2013).In addition a case control study conducted in Manchester on determinants of HPV and CIN3 in smoking and sexual behaviour has shown a significant increased risk with smoking (OR=2.20 95% CI: 1.44-3.35)(Deacon et al., 2000).In a multi- centric pooled analysis on smoking and cervical cancer in four different continents, results demonstrated an increase in risk of cervical cancer on HPV positive women who have ever smoked (OR 2.17 95%CI 1.46–3.22)(Plummer M, Herrero R, Franceschi S, 2003).An EPIC cohort has shown that with reference to never smoked , current , past and ever smoked has a two-fold increase in risk of developing carcinoma in situ or cervical intraepithelial neoplasia(OR:2.4 ;95% CI:1.7-3.2)(Roura et al., 2014).

5.3 Limitations

One of our limitations was there was no control group to compare the same risk factors in order to assess whether the same risk factors affected the other group. Also colposcopy and biopsy were not done as a confirmatory method for the positive lesions therefore false positives and negatives could not be ruled out. In addition, comparison of the lesions was

difficult as they were not grouped into low grade or high grade or undifferentiated. Findings were subjective to the individual screening the participants as different screeners have different views as there is no standard protocol for results. It is a cross-sectional study and was confined to only one ART center in the country therefore generalizing our findings will be difficult and also allows confounding and determination of temporary relationships is difficult.HPV genotyping was not done therefore the prevalence was not known. Furthermore, the study may have been exposed to information bias as responses were dependent on participants self-report.

CHAPTER SIX

CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Cervical dysplasia leading to cervical cancer remains a public health challenge and screening using VIA which involves see and treat approach is the most feasible and cheapest method for a third world country like the Gambia. Our study has demonstrated a prevalence of 21.7% which is higher than other prevalence in the sub-Saharan region, and it has shown independent risk factors of cervical dysplasia which includes age of participant, age at first sex, age at first birth/delivery and parity.CD4 count, WHO clinical staging and contraception were not significantly associated with cervical dysplasia. The current CD4 count of > 200 mm^3 and HAART use were found to be protective though not statistically significant .Therefore there is need for the in cooperation of cancer screening as part of the HIV care as it is paramount in HIV management.

6.2 Recommendation

1. National AIDS secretariat with the ministry of health and social welfare and other stakeholders should implement protocol on regular cervical cancer screening (VIA) on all HIV infected women in all HIV or ART centers.
2. The ministry of health and social welfare should encourage more studies or researches on HIV and cervical pre-cancer and cancer issues.
3. Health care providers with assistance from the reproductive and child health unit (RCH) in collaboration with the ministry of health and social welfare should create awareness and sensitization on the importance, availability of the cervical cancer screening, and its treatment to alleviate burden.

4. Early commencement of HAART treatment on all HIV infected women by ART centers.

5. Ministry of health and social welfare should endeavor to train more cytologists and pathologist as pap smear should not be replaced by VIA as both have different sensitivity and specificity levels.

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APPENDICES

Appendix I: Questionnaire

	PATIENT'S CONSENT		
	INTRODUCTION I am Dr. Anna H.Jammeh, an MPhil Resident at the University Of Ghana, School Of Public Health. I am doing a research on cervical dysplasia and associated Risk factors among HIV –Infected women attending hands – on care center in Brikama. This study will help the ministry of health and other stakeholders to ensure more HIV positive women are referred for cervical cancer screening as part of their routine care at the HIV clinic and formulate policies for its integration as a routine care for women. I assure you that the information will be treated with total confidentiality and your information will not be shared to any third party. Your participation in this research is entirely voluntary, and you may choose to withdraw at any stage of the interview if you wish .It will take between 10-15mins of your time. Thank you for your patience. SIGN/THUMB PRINT…….		
	Question	Code	question
	Questionnaire ID	QID	Interview code
	Question number	QN	
	Date		
Q NO.	**QUESTIONS**	Coding categories	CODES
Section A: Demographic characteristics of respondents			
1	Age of respondent	……years	AGE
2	Educational level of Respondents	No formal education……1 Primary……….2 Secondary and above……..3	EDU

3	Marital status	Single……...…1	MARSTAT
		Married……...…2	
		Divorced ……..……..…….3	
		Widowed…….……..4	
4	If ever married, type of marriage	Monogamous……..…1	MARTYPE
		Polygamous……...….2	
5	Occupation	Unemployed……..1	EMPLOY
		Formal…….2	
		Informal/self-employed…..……3	
6	Religion	Christian……...1	RELIGION
		Muslim…….2	
		Others specify……3	
SECTION B:REPRODUCTIVE RISK FACTORS			
7	Age at first intercourse	……years	AGECOIT
8	Age at first birth	…….years	BIRTH AGE
9	Do you have children	1……Yes	CHILDREN
		2…….NO	
10	If yes how many do you have	1 to 3……...1	PARITY
		4 to 6…….2	
		>7……...3	
12	Number of life time sexual partners		PARTNERS
13	Have you ever used contraceptives before?	YES ……... 1	CONTRACEPT
		NO ……..2	
14	If YES which type	Pills……..1	
		Depo provera……2	
		implanon/Jadelle/IUCD…..…3	CONTRATYPE
		Condom……4	

15	If yes for how long	……	CONTRALGHT
16	Have you ever used tobacco in any form?	1…….Yes 2……No	TOBACCO USE2
17	When were you diagnosed with HIV	……..……....years	WHENDIAG
18	No of CD4+ Cell count	……. CD4+ Baseline ……CD4+ current	CD4+
19	WHO staging:	Stage 1……...1 Stage 2……...2 Stage 3……...3 Stage 4……...4	STAGE
20	HAART Use	1……yes 2……No	HAART
21	If yes, what HAART regimen	First line ……1 Second line ……..2	HAARTREGIMEN
22	Have you ever had cervical cancer screening procedure done?	1……Yes 2……..No	PRESCREEN
23	If yes what was the result	Positive ……..... 1 Negative ……..2	PRESCRRESULT
24	Current VIA results	Positive……..1 Negative……2	CURRESULTS

Appendix: II: Consent Form

Research Title: CERVICAL DYSPLASIA AND ASSOCIATED RISK FACTORS AMONG HIV-INFECTED WOMEN ATTENDING HANDS –ON CARE MEDICAL CENTRE BRIKAMA, THE GAMBIA

Principal Investigator: Dr. Anna Jammeh, MPhil Resident, school of public health, University of Ghana

Supervisor: Dr. Ernest Kenu, Director of GFELT, Lecturer, School of public health, University of Ghana, Legon.

INTRODUCTION

I am Dr.Anna H.Jammeh, a Masters student from the University Of Ghana at School Of Public Health. I am doing a research on cervical dysplasia and associated Risk factors among HIV –Infected women attending hands –care center in Brikama. I am going to give you information related to the research and invite you to be part of this research.

Purpose of the research

The purpose of this study is to determine the proportion of abnormal cervical dysplasia and associated risk factors in HIV –infected women. This study will be useful by providing information that can be used to improve services to ensure more HIV positive women are referred for cervical cancer screening services as part of their routine care at the HIV clinic and even implement the integration of these services and as a result, more women will benefit from the screening once the routine screening is implemented in the routine care of HIV infected women.

The participation in the study will provide an opportunity for women to know their per-cancerous state .Women identified as having positive VIA results will be treated

immediately with cryotherapy and advanced cases will be referred Edward Francis Small Teaching Hospital for colposcopy and further specialist management.

PROCEDURE

Questions will be asked about yourself, your sexual history, information about your HIV status such as use of ART or not, duration on HAART, if first line or second line drugs, and the number of CD4 cell count from your file. A VIA will be done for you and the procedure will involve, lying in a supine position on an examination couch both feet place on metal stirrups to spread legs apart and also to flex the knees, buttocks are also positioned to the edge of the bed to enable easy examination and have a clear view of the vagina.. After proper positioning, with worn sterile surgical gloves, examination for any vaginal discharge will be done, external genitalia and perineal region will also be examined for any signs of excoriations, edema, vesicles, papules, sores, ulcerations, warts and swellings.In the presence of a good source of light focused in the vagina, a sterile warm Cusco's speculum is then inserted through the vagina to reach position and visualise the cervix. As the speculum is gently opened and the lips are fixed, the cervix comes into view and inspection is done for any abnormalities and identification of the external os and the transformation zone (squamocolumnar junction), findings are noted and all secretions will be gently wiped off.

A 5% acetic acid will be freshly prepared (5% acetic acid is prepared by adding 5 ml of acetic acid into 95 ml of distilled water) which will be gently applied on the visible cervix using a cotton swab soaked in acetic acid, the swabs after used will be disposed in a waste bucket, after 1min of application, observation for the appearance of white lesions on the transformation zone close to the squamocolumnar junction and results will be read

immediately. Results will be reported as either positive of negative depending on the findings.

Benefits

The benefit derived in this particular research is knowing your status if you have precancerous lesions or not and any positive lesion will treated immediately with cryotherapy and followed by regular follow ups for monitoring of treatment.

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. You may change your mind later and stop participating even if you agreed earlier.

Confidentiality

We will protect the information provided by you. A code will be used on the questionnaire and your name, or address will not appear anywhere in the reports. After data collection all questionnaires will be securely stored and access will be to the principal investigator only.

Right to withdraw

You do not have to take part in this research if you do not wish to do so. You may also stop the interview at any point if you so wish to. It is your choice and all of your rights will still be respected.

CONTACT INFORMATION:

If you have any question, you may contact:

Anna H. Jammeh :(0240971454),

Dr. Ernest Kenu of the school of public Health: (0208826008).

INFORMED CONSENT FORM

I confirm that the information above was read and explained to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I hereby consent to participate as a participant in this research.

Name of Participant_____ Signature of Participant/Thumb print

Date _____ Day/month/year

Statement by the researcher

I confirm that the participant was given an opportunity to ask questions concerning the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

Name of researcher----------

Signature---------- Date --------/-------/-------Day/month/year