Cost-Effectiveness Analysis of Integrating Cervical Cancer Screening Into HIV-Care in Uganda

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Master Thesis

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May 2017

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2017

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http://www.duo.uio.no/

Trykk: Reprosentralen, Universitetet i Oslo

ABSTRACT

Background- Uganda is one of the countries with a high economic burden of both cervical cancer and HIV/AIDS. These two diseases share the same risk factors and women with HIV/AIDS have two to twelve chances of suffering from cervical cancer. Therefore, to minimise this risk there is a need to integrate cervical cancer screening into HIV care. However, for optimal allocation of resources and effective decision making the Cost-Effectiveness Analysis (CEA) of integrating these two services needs to be established. This is what formed the gist of the investigation.

Aim of the Study- To estimate the Cost-Effectiveness Analysis of Integrating cervical cancer screening into HIV care in Uganda.

Method- Patient data was collected using Retrospective Review Chart. Using this method, 20,000 patient folders were reviewed and 16,366 folders met the study criteria of which 2,065 HIV positive women had received cervical cancer screening from 2012 to 2016. Only costs incurred from the provider perspective were included in the study. The differences in costs of screening the entire population and the costs incurred under voluntary screening (status quo) were divided by the differences in total life-years gained from screening the entire population and life-years gained under status quo. The effect of uncertainty on model parameters was examined by conducting a probabilistic sensitivity analysis.

Results- The patient characteristics in the study that were associated with cervical cancer included: age of HIV positive women screened, status of Antiretroviral therapy and the CD4 count. These were assessed at the bivariate and multivariate stages. At both stages, it was revealed that age and CD4 count were statistically significant to the cervical cancer screening among HIV positive women. However, the status of antiretroviral therapy was not statistically significant to cervical cancer screening outcome. The cost-per-positive-screening result among HIV positive women was 50 USD. The Incremental Cost-Effectiveness Ratio of 46.5 per life-year gained from cervical cancer screening was estimated. However, the study used a 5-year survival probability estimate of cervical cancer from a Tanzanian study to conclude that the integration of cervical cancer into HIV-care in Uganda was cost-effective. This is because the survival probability estimates of cervical cancer in Uganda have not yet been estimated.

Conclusion- The integration of cervical cancer screening into HIV care is highly cost-effective and it has the potential to prevent High-Grade precancerous lesions from progressing into cervical cancer among HIV positive women.

Key Terms: Cervical cancer, Incremental Cost-Effectiveness Ratio, Screening, Uganda

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ACKNOWLEDGEMENT

First and foremost, I would like to thank my loving Creator for making me a curious being who loves to explore His creation and for giving me the opportunity to write this thesis. Without Him, I can do nothing.

The success of this project required a lot of guidance and assistance from many people and I am extremely fortunate to have got this all along to the completion of my master thesis. Whatever I have done is only due to such guidance and assistance and I would not forget to thank them.

I respect and extremely thank my supervisor, Associate Professor Tron Anders Moger for the guidance, supervision and the help given to me throughout the entire process of writing this research project. I have learned a lot from your academic experience. I am very grateful for your lasting intellectual influence on me.

I would like to express my eternal appreciation to my dearest parents who have always been there for me even at the time when I least expected their support. May the Almighty Lord bless you abundantly for the priceless sacrifices you have made.

I heartily thank 'Taata' Ibrahim Kasiita for your financial and moral support given to me during my entire period of my studies.

I would like to express my eternal appreciation to my girlfriend Vanessa for the love, care and support you gave me during this entire academic journey.

I owe my profound gratitude to my dear brothers and my lovely my sisters for your unlisted encouragement and sacrifices that you have made for during the time of my study.

I extend my sincere appreciation to my classmates Pascale, Enock, Abraham and Edem for academic knowledge we shared throughout the learning process.

I extend my sincere gratitude to Harriet Chemusto, Alex Riolexus Ario, Susan Nakubulwa, Maria Sarah Nabaggala, Kushie Jackie and the entire staff at Mildmay- Uganda for the for the assistance you gave during the process of data collection.

DEDICATION

I dedicate this master thesis to my academic advisor Birthe Neset.

LIST OF ABBREVIATIONS

ACCP	American College of Clinical Pharmacy
ART	Antiretroviral Therapy
ASE	Attitude, Social Norm, Self-Efficacy model
APHRC	African Population and Health Research Center
AIDS	Acquired Immune Deficiency Syndrome
BLR	Binomial Logistic Regression
CEAC	Cost Effectiveness Acceptability Curve
CDC	Center for Disease Control and Prevention
DNA	DeoxyriboNucleic Acid
GDP	Gross Domestic Product
HIV	Human Immunodeficiency Virus
HSILs	High-Grade Squamous Intraepithelial Lesions
HPV	Human Papilloma Virus
ICER	Incremental Cost-Effectiveness Ratio
ICWEA	International Community of Women living with HIV Eastern Africa
IRB	Institutional Review Board
IARC	International Agency for Research on Cancer
LEEP	Loop Electrosurgical Excision Procedure
LSILS	Low-grade Squamous Intraepithelial Lesions
LMICs	Low and Middle Income Countries

NCHE	National Council of Higher Education
MoH	Ministry of Health
STIs	Sexually Transmitted Infections
UAIS	Uganda AIDS Indicator Survey
UBoS	Uganda Bureau of Statistics
UNAIDS	Joint United Nations Programme on HIV/ Acquired Immune Deficiency Syndrome
UNDP	United Nations Development Programme
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
USD	United States Dollar
VIA	Visual Inspection with Acetic acid
WHO	World Health Organisation

1 PREAMBLE

Cervical cancer is the third most common cancer among women worldwide. It is the fourth leading cause of cancer deaths in women, with an estimated 270,000 deaths annually. Over 85% of both cervical cancer cases and deaths occur in developing countries (Lancet 2010; Gakidou, Nordhagen & Obermeyer, 2008). In Sub-Saharan Africa, cervical cancer represents 22% of all cancers in women (Parkin, Ferlay, Sitas,Thomas, Wabinga & Whelan, 2003).

Similarly, Sub-Saharan Africa has the highest prevalence, incidence and mortality rates of Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome (HIV/AIDS) epidemic in the world. In 2013, it was estimated that 24.7 million people were living with HIV and this accounted for 71% of the global total number of people infected with HIVAIDS. More so, women are most affected with HIV/AIDS. They account for 58% of the total number of people living with HIVAIDS in Sub-Saharan Africa (UNAIDS, 2013).

Further access to Antiretroviral Therapy (ART) has improved lives of least 11.7 million patients in Low and Middle-Income Countries (LMICs). This has led to the reduction in the annual number of new HIV infections among adults in Sub-Saharan Africa which have declined by 34% since 2001. Mills (2011) noted that ART increases the life expectancy of HIV positive women in Uganda aged 35 years by 22 years. This is comparable to the life expectancy of HIV negative women which is 58.6 years (UNDP, 2016). This explains why the number of AIDS-related deaths fell by 39% between 2013 and 2013 (UNAIDS, 2013; Kerry 2011). Before the introduction of ART, lack of cervical cancer screening among HIV-infected women probably had little influence on their life expectancies because of the high competing mortality associated with other causes, but the situation is changing rapidly everywhere. For instance, by 2005 at least 400, 000 HIV infected women had received ART in Sub-Saharan Africa (Franceschi & Jaffe, 2007).

However, the deliberate government efforts, coincident with unprecedented global commitment for HIV funding and support from various donor organizations such as Global Fund that has led to tremendous advances in treatment, prevention and care especially in countries like South Africa, Botswana and Uganda which are likely to be undermined by cervical cancer. There is strong evidence of a synergistic relationship between the two diseases. HIV-positive women are 2–12 times more likely to develop pre-cancerous lesions that can develop into invasive cervical cancer if no timely screening and treatment

interventions are provided. Women infected with HIV face an increased risk of persistence and recurrence of human papilloma virus (HPV); and HIV infection is associated with a higher risk of invasive cervical cancer, an AIDS-defining disease (Gakidou, Nordhagen & Obermeyer, 2008). Thus, this explains why there is a need for Sub-Saharan countries with high prevalence of HIV/AIDS to develop cost-effective approaches to integrate cervical cancer screening into HIV.

1.1 Burden of Cervical Cancer and HIV/AIDS in Uganda

Uganda is one the countries with a huge economic burden of both HIV and AIDS and cervical cancer. The incidence and mortality rates for cervical cancer are estimated to be 45.6 per 100,000 women and 25 per 100,000 women respectively (Sankaranarayanan & Ferlay 2006; Parkin et al., 2002). More than 80% of women are diagnosed with late-stage disease, which is expensive to treat and its chances of survival are extremely low. For example, 5-year relative survival for cervical cancer is estimated at 17.7% in Uganda (Gondos, Brenner, Wabinga, & Parkin,2005). It accounts for 40% of all cancers in Uganda and is the leading gynaecological cause of death in Ugandan women (Strategic Plan for Cervical Cancer Prevention and Control in Uganda, 2010).

Uganda was among the first countries to acknowledge the presence of the disastrous HIV/AIDS epidemic in the early 1980s (National HIV Prevention Strategy, 2011-2015). Since then, at least 2.5 million people in the country have lost their lives due to HIV/AIDS. Between 2007 and 2013, the estimated number of people living with HIV increased from 1.2 million to 1.6 million of which women accounted for over 58% of the total number of HIV and AIDS patients (HIV and AID Uganda Country Progress Report, 2013; UNAIDS, 2013).

The prevalence of HIV/AIDS remains higher among women than men. For example, according to the Uganda AIDS Indicator Survey (UAIS) (2011) the prevalence of HIV among women was estimated to be 8.3% compared to 6.1% among men. Similarly, the epidemiology survey carried out by International Community of Women Living with HIV/AIDS in East Africa (ICWEA) (2015) noted that the HIV prevalence was higher among women than men by the ratio of 7:3:6.

According to the study carried out by Michael (2008) to determine the prevalence of cervical cancer among HIV/AIDS positive women in Rakai District. Out of 926 women infected with

HIV/AIDS almost 50% had strains of human papilloma virus (HPV) that is associated with a risk of cervical cancer. The same study showed that women who reported symptoms of tuberculosis, shingles or oral thrush, all of which are associated with HIV, had an increased risk of infection with potentially cancer-causing HPV strains. A multivariate analysis showed that HIV was independently associated with the presence of potentially cancer causing HPV strains.

According to Kumakech, Andersson, Wabinga & Berggren (2014) majority of the healthcare providers (HCPs) and policymakers in Uganda affirmed that much pessimism exists regarding the feasibility of HIV and cervical cancer screening integration. However, majority of the HIV and AIDS clinics in Uganda remain non-integrated and do not offer cervical cancer screening to their clients. More so, almost all the cervical cancer screening centres in Uganda do not offer HIV testing. This implies that many HIV positive women miss the opportunity of receiving screening at the same HIV and AIDS centres. This increases the woman's risk of presenting invasive cervical cancer which is very difficult to treat.

Both HIV and HPV are Sexually Transmitted Infections (STIs) and so share the same risk factors, such as early age at sexual debut, multiple sexual partners, and condom use. This explains why Jean, Enriquito Lu, Harshad, Sharon, Anjanique (1997) noted that countries where cervical cancer rates are highest often have high prevalence of HIV. The presence of HIV increases the risk of cervical pre-cancerous changes which considerably true with reference to Uganda.

These findings reveal that women in Uganda are adversely affected with HIV and cervical cancer. This explains why the World Health Organization (WHO) recommends a more aggressive cervical cancer screening and treatment schedule for HIV-positive women. Despite, the high economic burden of both cervical cancer and HIV/AIDS in Uganda, the integration of cervical cancer screening into HIV care has not fully taken off within various HIV care centres. Integrating cervical cancer screening into HIV care should include access to information, education, communication, screening, and treatment in a single-visit approach (WHO, 2015).

The optimal and most cost-effective method of screening, treatment, and integration has not yet been evaluated. If the efficacy, cost-effectiveness, and financial sustainability of integrating cervical cancer screening programs into HIV care can be proven, then the optimal

models could potentially be scaled across the country where HIV and cervical cancer represents a large public health burden. This could address women's multiple needs at once, and could potentially increase cervical cancer screening rates, improve program efficiency, and ultimately reduce the number of women who develop cervical cancer in country where the economic burden of cervical cancer is enormous (Agurto et al, 2005).

It is against this background that this study has been designed to determine the cost-effectiveness of integrating cervical cancer screening into HIV care in Uganda. No similar study has been carried out in Uganda.

1.2 Justification of the Study

Cost-effective health care interventions within an integrated healthcare system are one of the aspects of The Second National Health Policy (2010). This is viewed as an economical approach amidst the various healthcare challenges that the country is facing.

For instance, Uganda faces an enormous dual economic burden of HIV/AIDS, cervical cancer among women and malaria. Several studies have recommended the integration of cervical cancer into HIV/AIDS care as a feasible approach that would save lives of many HIV women who are at a risk of suffering from cervical cancer. However, the cost-effectiveness analysis of this approach in respect to the provider and society perspective has not been estimated. This demonstrates why it is important to conduct a cost-effectiveness study to provide sufficient answers to these questions;

Which screening intervention is cost-effective? What would be the implications of scaling the program up or down in terms of costs and cost-effectiveness? What would be the costs of replicating the program's activities in different parts of the country? How would the costs affect the results and the eventual sustainability of the program? What is the cost of each life-year gained from the treatment of pre-cancerous lesions using cryotherapy?

1.3 Objectives of the Study

The main objective of this study is to determine the cost-effectiveness of integrating cervical cancer screening with HIV care in Uganda. Specifically, to compare the institutional costs of screening all HIV positive women at Mildmay-Uganda to the status quo.

More specific objectives

1) To ascertain if age, HIV treatment and CD4 count predicts a positive cervical cancer result.
2) To evaluate the cost per positive screening result among women among HIV positive women.
3) To estimate additional cost of screening all compared with status quo.
4) To estimate the cost per life year gained from cervical cancer screening among HIV positive women

1.4 Structure of the Thesis

The overall structure of the thesis is as follows:

Chapter One discusses the economic burden of HIV-AIDS and cervical cancer in Sub-Saharan Africa and more specifically in Uganda. The objectives of the study are also outlined as well as the justification of the study.

Chapter Two presents the review of the literature. This includes; the pathogenesis of cervical cancer, the various methods of prevention. Specific reference is given to the trends of cervical cancer screening in Sub-Saharan Africa and the factors associated to this phenomenon. Furthermore, the relationship between cervical HIV/AIDS was discussed to ascertain the logistic relationship between cervical cancer and CD4 count as stated in the objective section. Studies relating to the feasibility, effectiveness and cost-effectiveness integrating cervical screening are examined.

Chapter Three, discusses the social-economic status of Uganda. It explicitly presents the structure of the healthcare system, the health policy the drives the healthcare sector and how this policy is financed. The implication of the healthcare financing towards access of care and general challenges facing the healthcare sector are discussed in this chapter.

Chapter Four, presents the methods of data collection and research design. Description of the intervention, estimation of costs of the intervention, defining and measuring of health effects, cost-effectiveness analysis and sensitivity analysis are presented in this chapter.

Chapter Five, presents the research findings. These include; the summary of the screening patterns of cervical cancer at Mildmay-Uganda from 2012 to 2016, description of the patient characteristics, cost estimates of the intervention, estimation of the cost-effectiveness analysis and the results from logistic investigating the relationship between cervical cancer and HIV/AIDS. The cost-per-positive-screening result, cost-per-life-year-gained is also presented in this chapter.

Chapter Six, discusses the results, presents the limitations of the study and related studies, the ethical considerations, recommendations and the conclusion.

2 LITERATURE REVIEW

2.1 Preamble

The purpose of this chapter is to review literature pertaining to cost-effectiveness of integrating cervical cancer screening into HIV-care and the various components therein. It is important to appreciate, as stated earlier, that in the search to answer the main research question, the researcher developed several research objectives to be answered in anticipation that, by answering them, the main research question would be answered. The literature reviewed was deemed necessary to answer the research objectives. Subsequently, the research questions formed the content of the literature review progression in this study. The literature reviewed was accessed through the electronic library of the University of Oslo. Journals were obtained by using search engines such as National Centre for Biotechnology Information, PubMed, WHO, American College of Clinical Pharmacy (ACCP) and Ministry of Health (MoH) publications among others.

The researcher considers the literature because it provided a clear and multi-dimensional understanding of the study question. Specifically, the literature review sections consist of five broad parts. The first part discusses the origin of cervical cancer. The second part discusses the prevention of cervical cancer screening which entails primary and secondary prevention. The third part discusses the overview of cervical cancer screening within Sub-Saharan countries and the fourth is the continuation which discusses the factors relating to the up-take of cervical cancer screening within Sub-Saharan countries. The fourth part endeavours to explain the relationship between cervical and HIV/AIDS and it is from this scientific relationship that cost-effectiveness analysis of integrating cervical screening into HIV care is drawn. The last part of the literature view entails studies relating to the feasibility, acceptability and cost-effectiveness that have been conducted regarding integrating cervical cancer into HIV care.

2.2 Pathogenesis or Origin of Cervical Cancer

Cancer begins with a change in the structure of the DeoxyriboNucleic Acid (DNA) which is present in all human cells. DNA provides the cells with a basic set of instructions, including when to grow and reproduce. An alteration in the DNA structure is known as mutation. It alters cell growth and the cells out-grow instead of stopping when they should. When this process occurs, then the cells reproduce uncontrollably and produce a lump of a tissue known as a tumour. The word tumour refers to a mass and this is a general term can refer to benign (generally harmless) or malignant (cancerous) growth. Benign tumours are non-malignant or non-cancerous tumours. A benign tumour is normally localized, has not yet spread to other parts of the body and many of them respond to treatment. However, if left untreated, it will enlarge and this can lead to serious diseases. Malignant tumours are cancerous growths. There are resistant to treatment, may spread to other parts of the body and they sometimes recur. (Nair & Peate, 2013).

Explicitly cervical cancer occurs when there is an abnormal cell growth in the cervix. The cervix is the lower part of the uterus that connects the body of the uterus to the vagina or birth canal (WHO, 2013). Cervical cancer originates from a sexually transmitted disease through a genital contact with an infected person transmitted by HPV which grows silently in the cervix and may later develop into invasive cervical cancer (Bomela & Stevens, 2009; Cox, 2006). A woman's risk of developing cervical cancer is determined in part by her risk of having been exposed to HPV. Approximately 90% of HPV infections clear within two years with no symptoms, the remaining 10% of HPV infections that persist can progress to cervical cancer. Many of these cases are relatively stable and can be eliminated by the body own immune system however in situations where the body fails do so then cervical cancer will develop (Shuti, 2010).

Most cervical cancers begin in the cells lining the cervix. Normal cells of the cervix usually first develop pre-cancerous changes which may progress to cancer, although in many cases these changes do not result in progression to cancer (Burd, 2003). For infection to occur, the virus must have access to the basal epithelial cells, either in epithelium that is naturally thin and immature, such as the transformation zone of the cervix or the anal verge, or through microscopic tears or abrasions in the external genital skin or the introital or vaginal mucosa (Cox, 2006). Thus, for cervical cancer abnormalities to surface, the virus must become integrated into the host genomic DNA

The HPV has been associated with invasive cervical cancer as well as advanced precursor lesions known as Cervical Intraepithelial Neoplasia (CIN). CIN is a premalignant condition of the uterine cervix (Levine, 2005). These are characterised by the appearance of abnormal cells on the surface of the cervix. CIN is classified into grades I, II and III depending on the proportion of the thickness of the epithelium showing mature and differentiated cells. CIN I signify mild dysplasia and is classified as Low-grade Squamous Intraepithelial Lesions (LSILS).

CIN II and III includes moderate to severe dysplasia and these are classified as High-Grade Squamous Intraepithelial Lesions (HSILs) (Jin, 2010). More severe grades of CIN (II and III) reveal a greater proportion of the thickness of the epithelium composed of undifferentiated cells (Odendal, 2011). Thus, CINs II and III encompasses a moderate-to-severe dysplasia.

Jin (2010) contends that most of LSIL automatically resolve, whereas HSILs are more inclined to develop into invasive cervical cancer. The latter is consistently detected at an average age of 10 to 15 years younger than that of invasive cervical cancer. Most epidemiological studies assert that at least 76% of the cases of CIN are attributed to HPV infections. However, some lesions will continue to grow and may eventually develop into cancer. Most precancerous lesions will regress back to normal and only a small proportion will progress to invasive cervical cancer (Kahesa, 2012).

Furthermore, Kahesa (2012) stated that about 11% of CIN I will progress to CIN III, while 20% of CIN II will progress to CIN III and the possibility is greater for high grade lesions to progress to invasive cancer. It is estimated that the time frame for a woman with persistent oncogenic HPV infection until cervical cancer has evolved is about ten years or more, depending on other predisposing factors. Invasive cervical cancer develops after a long period of time from well-defined precursor lesions. The average age at presentation and rates of progression of these precursors are related to their histopathologic and cytologic grade.

These reasons form benchmark to explain why it is necessary to have appropriate and timely cervical cancer screening programs and more so encourage women access them. However, the distinction between CIN II and both CIN I and CIN III in biopsy specimens is complicated by the fact that the thickness of the epithelium occupied by neoplastic basaloid cells and mitotic figures often varies greatly within any given cervical biopsy specimen. While variations in the

angle at which the epithelium has been cut during histological sectioning can also have an effect (IARC, 2005).

2.3 Prevention of cervical cancer

Cervical cancer provides a unique public health and epidemiologic opportunity in contrast to most other cancers; it can be prevented at both primary and secondary levels. Primary prevention is based on vaccination for girls aged 11 and 12 years. Secondary prevention entails screening programs designed to identify and treat precancerous lesions referred to as high-grade squamous intraepithelial lesions (HSIL) (Kahesa, 2012; Denny&Wright, 2009).

2.3.1 Primary prevention

Primary prevention of cervical cancer is essentially based on healthy lifestyles and vaccination against HPV. Health lifestyle involves a behavioural change which includes; abstinence from sexual exposure, being mutually faithful, and consistent use of condoms. (Kahesa, 2012).

Vaccination encompasses the use of prophylactic or preventive vaccination against the HPV (types 16 and 18) which is the major cause of cervical cancer (Grcea, 2014). The two types of vaccines that are currently available against HPV infection include quadrivalent vaccine which prevents HPV genotypes 6, 11, 16 and 18 and bivalent vaccines that prevents genotypes 16 and 18 (WHO, 2008). These two vaccines have been validated to be effective in the prevention of persistent infection caused HPV types 16 and 18. The quadrivalent vaccine also provides protection against the two low risk HPVs known to cause most anogenital warts (Kahesa, 2012).

However, the cost of the available HPV vaccines remains very high and far is beyond the affordable means of the majority population and public authorities in many African countries. The average cost of the three doses needed is estimated at about 400 USD, which poses a dilemma to universal access to the vaccine and a challenge to the sustainability of any primary prevention policy based on large-scale in low resource countries where the economic burden of the disease is devastating (WHO, 2008).

2.4 Secondary prevention of cervical cancer

This entails screening. Systematic screening, treatment programmes and effective HPV vaccination provides the best interventions for preventing cervical cancer among HIV women (WHO, 2012). The American College of Obstetricians and Gynaecologists defines cervical cancer screening as an approach that is used to find changes in the cells of the cervix that could eventually lead to cervical cancer. The objective of cervical cancer screening programmes is to reduce the mortality from (and incidence of) the disease by identifying women with precancerous cervical lesions and early invasive cancers, and treating these women appropriately.

Currently, cervical screening is acknowledged as the most effective approach for cervical cancer control. The success of any screening programme pivots around the functioning of that programme in its comprehensiveness. The requirements to attain universal screening include; the ability of a programme to ensure high levels of coverage of the target population, offer high quality caring services, develop and monitor good referral systems that ensure good patient follow-up and ensure that the patients receive appropriate, acceptable and caring treatment in the context of informed consent (WHO, 2002). However, majority of the Sub-Saharan countries do not possess the facilities to meet these requirements which partly explains why economic burden of cervical cancer is still high within these countries.

In low resource setting, the optimal age- group for cervical cancer screening that achieves the greatest public health impact is between 30-39 years of age. Screening programmes can lead to a significant reduction in the morbidity and mortality associated with this cancer. Several studies have indicated that if a woman aged 35-year-old screened only once in her life, a single-visit or two-visit approach with the VIA method; this could reduce the lifetime risk of cervical cancer by 25% and HPV DNA testing could reduce it by 36% (Sherris, Wittet, Kleine, Sellors, Luciani, Sankaranayanan & Barone, 2009).

However, screening is only effective if there is a well-organized system for follow-up and treatment for women with abnormalities. This is done to prevent the development of cancer or to treat cancer at an early stage (WHO, 2002). Unfortunately, the fragmented nature of various healthcare systems in developing countries has retarded systematic cervical cancer screening since it does not provide follow-up after screening especially for those patients sent to referrals. Secondly, the treatment of cervical cancer is extremely expensive for many low-

income households. Thus, overall improvement healthcare systems has a big impact towards ensuring better screening outcomes.

Several tests can be used in screening for cervical cancer namely; The Pap smear (cytology), Visual Inspection with Acetic acid (VIA) or Lugol's iodine (VILI)and the new methods of using human papillomavirus (HPV) DNA testing (Sherris et al, 2009).

2.4.1 Cytology screening in middle-income countries

Cytology-based screening involves using either conventional cervical cytology (Pap smears) or liquid based cytology. These entail the collection of cell samples from the cervix followed by slide preparation, staining, reading and reporting. This procedure requires a doctor or a nurse to gather the samples; sufficient and consistently available supplies and equipment must be provided to collect and process the smears (Sherris et al, 2009). This implies that cytology based screening requires well-established health systems which are non-existent in many developing countries.

Furthermore, cytology screening process is associated with the delays between screening, provision of test results and ultimate treatment make it less likely that test positive women will ever receive their results in low resource countries (WHO, 2012; Sherris et al, 2009). The challenges to implement sustainable and feasible cytology-based programs in low resource countries have inspired researchers to seek promising alternatives to Pap smear screening with referral of women with positive results for colposcopy.

2.4.2 Visual Inspection with Acetic acid (VIA) or Lugol's iodine (VILI)

VIA involves performing a vaginal speculum examination. A healthcare provider applies dilute (3-5%) acetic acid (vinegar) to the cervix. It entails viewing the cervix with the naked eye to identify colour changes on the cervix so that the healthcare personal can determine whether the test is positive or negative for possible pre-cancer lesions. Acetic acid is used to enhance and mark the acetowhite change of pre-cancer lesions or actual cancer and variations in pre-cancer cell proteins make abnormal cells temporarily appear white when exposed to vinegar (ACCP, 2003).

The infrastructure needed for VIA is quite simpler compared to pap smear or any other cytology based screening. It requires private exam area, examination table, trained healthcare professional, adequate light, sterile vaginal speculum, new examination gloves, or HLD surgical gloves, large cotton swabs, dilute acetic acid, small bowl containers with 0.5% chlorine solution, plastic bucket with a plastic bag and quality assurance system to maximize accuracy. These items were used to estimate the cost of screening one woman for this study.

Quality assurance entails, but not limited to, periodic supervision, refresher training, program monitoring and evaluation and effective mechanism of constructive feedback from women and healthcare providers (ACCP, 2003). This explains why various (WHO, 2012), Sherris et al, (2009) have recommended the use of VIA within low resource setting environment.

The location of the acetowhite area should be considered in the final judgment call as whitish areas representing metaplasia. The squamocolumnar junction is the point at which columnar cells meet ectocervical squamous cells on the cervix. This junction marks the furthest extent of the transformation zone towards or in the cases of post-menopausal women into cervical canal. However, if no acetowhite or faint acetowhite lesions; polyp, cervicitis, inflammation, Nabothian cysts then this is regarded as test negative. When sharp, distinct, well-defined, dense (opaque/dull or oyster white) acetowhite areas—with or without raised margins touching the squamocolumnar junction (SCJ); leukoplakia and warts are seen then this is regarded as a test positive (AACP, 2002)

The management of test positive has two options namely; offering immediate treatment using cryotherapy and this should only treat lesions that occupy less than 75% of cervical cancer area that do not exceed the vaginal wall but also do not extend beyond the limits of cryotherapy. The test positive lesions that do not meet this criterion must be referred to facilities that offer other treatment options other than cryotherapy

According to ACCP (2003), the range of estimated sensitivity and specificity from seven cross-sectional studies specifically addressing the accuracy was between 65% to 96% and 64% to 98% respectively. However, other various cross sectional studies that have accessed the performance of VIA in terms of sensitivity and specificity in detecting high-grade dysplasia in low-resource settings have noted that it is at least equal to that of cytology, while the specificity of VIA is lower. However, when used on a wide scale clinical settings, the replicability of VIA is unknown (ACCP, 2012).

According to a meta-analysis in which 146 articles retrieved, 77 papers reported that 28, 827 cases of CIN were treated with cryotherapy attained a cure rate of 94% for CIN I. (Sauvaget, Muwonge & Sankaranarayanan, 2012). Similarly, Jacob et al (2005) asserted that cryotherapy has an overall cure rate of 89—91% at 1-year follow-up. Similarly, ACCP (2003) cryotherapy resulted in higher cure rates for less severe lesions (CIN I and CIN II) but it had lower cure rates for more severe lesions CIN III that tend to extend into the endocervical canal.

It is against these reasons that the WHO, IARC, APHRC and other stake holders have advocated for the use of VIA in many developing countries. The treatment of test positive result involves using cryotherapy. Women with CIN II are usually treated with cryotherapy.

2.4.3 HPV DNA-based screening methods

The HPV DNA test (known as the cobas HPV test), it is a diagnostic procedure that uses a small plastic spatula- or broom-shaped instrument to collect material from the cervix and vagina. The sample of cervical cells collected for the test allows doctors to identify 14 high-risk types of HPV, including HPV 16 and HPV 18 (American Cancer Society, 2014). The American Cancer Society does not recommend using the HPV DNA test to screen for cervical cancer in women who are under 30 years of age. This is because women in their 20s who are sexually active are much more likely to have an HPV infection that will go away on its own. For these younger women, results of this test are not as significant and may be more confusing.

Sherris et al (2009) noted that the use of HPV DNA testing followed by cryotherapy results in a greater reduction in the incidence of cervical cancer precursors than the use of other screen-and-treat approaches. However, it is relatively expensive, it involves sophisticated processing in a laboratory and the results become available only after seven hours.

The disintegrated health care system coupled with poor infrastructure in many developing countries has limited the use of cytology testing using Pap smear and HPV DNA screening method thus explaining why the use of VIA remains the most appropriate screening intervention for cervical cancer with low developing nations.

2.5 An Overview of Cervical Cancer Screening in Sub-Saharan Countries

The poor access to, and poor quality of, cervical cancer-prevention and control services has hindered the standardised screening, treatment and efficient HPV vaccination. The uptake of cervical cancer screening services among women remains very low and this partly explains why the most women present cervical cancer at an invasive stage whose survival rate is very low. Furthermore, this reveals why there is a huge disparity in morbidity and mortality of cervical cancer between high and low-income countries (WHO, 2010).

The laborious efforts by WHO, UNDP and other organisation to fight against cervical cancer mainly depend on the accessibility to screening. Several studies that have been carried out indicate that many majority women in Uganda and other developing countries have not accessed cervical cancer screening.

A study to investigate the utilization of cervical cancer screening and associated factors among women living in rural areas of Uganda found that out of the 900 women who were interviewed, only 43 (4.8%) had ever been screened for cervical cancer (Ndejjo, Mukama, Mauabyimana & Musoke, 2016). Only 21 women (48.8%) of these had done so because they had been requested by a health worker. Secondly, 17 (39.5%) had certain signs and symptoms which were associated with cervical cancer while 16 (37.2%) screened voluntarily to know their status. The study established that the primary barriers to cervical cancer screening were; negative individual perceptions which counted for 64.5% (553) and health facility related challenges 16.6% (142).

Furthermore, the similar study indicated that 416 respondents were not aware of the screening services (48.5%). The independent predictors to cervical cancer screening were; being recommended by a health worker [AOR = 87.85, $p<0.001$], knowing where screening services were offered [AOR = 6.24, $p = 0.004$], and knowing someone who had ever been screened [AOR = 9.48, $p = 0.001$]. The study concluded that the prevalence of cervical cancer in rural areas was low however it is imperative to improve access to health care services to enable more women access screening. More so, it reflected the urgency of health workers to counsel women about the advantages of cervical cancer screening within family planning and HIV centres where women come to seek medical care.

Cyprian, Twinomujuni, Nuwaha & Babirye (2015) used the ASE model which related to attitude, social influence and self-efficacy to identify factors associated with intention to

screen cervical cancer among women of reproductive age in Masaka District-Uganda. A descriptive community based survey included 416 women and revealed that only 29/416 (7%) of the respondents had ever screened for cervical cancer. A higher proportion of 262 women (63%) reported the intention to screen in the future. Like the previous study conducted by Ndejjo et al (2016), this study recommended that health education was an imperative aspect to improve women's attitudes towards cervical screening and addresses the unease held by the women who fail to turn up for screening. These studies indicate that health care workers play an influential role towards increasing the number of women seeking cervical cancer screening.

Similarly, Kamulegeya, Bukenya & Makumbi (2014) conducted a study to determine the uptake of cervical cancer screening among women aged 25-49 years in Nakasongola District - Uganda. A cross-sectional community survey of 526 women was interviewed. Only 77 women (14.6%) of the women reported to have screened for cervical cancer and 61 (79.2%) of these has done so within the district. Only 5 women (6.5%) had screened two or more times and their willingness to adhere to next screening appointment was almost universal. The above studies clearly indicate that the level utilization of cervical cancer screening among women in Uganda is very low.

Comparable studies carried out in Kenya unfolded that few women seek cervical cancer screening which partly explains why 4802 women are diagnosed of cervical cancer every year. Around 9.1% of women in the general population are approximated to harbour cervical HPV-16/18 infection at a given time and 61.4% of the invasive cervical cancer cases are attributed to HPV 16 or 18 (HPV Information Centre-Kenya, 2015). In the cross-sectional questionnaire survey conducted at Moi Teaching and Referral Hospital revealed that only 29.937 women out of 216 had ever received cervical cancer screening (Were, Nyaberi & Buziba, 2011).

Another cross-sectional survey involved 388 women seeking reproductive health services in Kisumu found out that 23.8 (6%) had been screened despite that fact 112.5 (29%) of 388 women had previously heard about cervical cancer. These mainly received this information from health workers (Sudenga& Rostich, Otieno & Smith, 2013)

In Tanzania, a cross sectional study sampled which 512 primary school teachers; only 108 (21%) had been screened for cervical cancer and the utilization of cervical cancer services

was about 28% among women aged 20-29 years (Kileo, Michael, Neke & Moshiro, 2015). These studies clearly indicate that very few women within the reproductive age seek cervical cancer screening among developing countries. This partly explains why many women within Sub-Saharan Africa present cervical cancer at a late stage whose prognosis is hard to treat. What factors account for this phenomenon?

2.6 Factors Related to Cervical Cancer Screening Uptake

The low levels of cervical cancer screening have become a public health concern and a number studies have been conducted to identify the barriers to effective utilization of cervical cancer screening in among Sub-Saharan Africa counties. Thus, it is important to discuss these impediments because understanding these factors could guide future educational and policy interventions to increase cervical cancer screening within cost-effective frameworks (Kileo et al, 2015). These include; inadequate access to health services, inadequate information regarding cervical cancer among healthcare workers, lack of awareness (Bingham et al, 2003).

2.6.1 Level of knowledge

Knowledge about cervical cancer and its risk factors among women is considered as a key factor that influences the uptake of screening. Women who have more knowledge about cervical cancer and its prevention are more likely to seek screening as compared to their counterparts who are ignorant about the disease.

In Uganda, Mutyaba, Mmiro & Weiderpass (2006) conducted a study among 285 healthcare workers at Mulago referral hospital and found out that less than 40 % of the respondents had knowledge about cervical cancer and its risk factors. About 231 (81%) of the respondents had never been screened for cervical cancer. Another study on influences on uptake of reproductive health services in Nsagi community and their implication for cervical cancer screening found out that ignorance about cervical cancer and its risk factors was one of the barriers to screening (Mutyaba, Faxelid, Mirembe & Weiderpass, 2007).

Similarly, a study conducted in Zimbabwe in which 356 women were interviewed from Mutoko & Shurugwi revealed that 95.78% of the respondents had never gone for cervical cancer screening and they had little knowledge about the key aspects of the disease namely;

causes treatment and prevention. Therefore, massive sensitization of women about cervical cancer was highly recommended (Mangoma, Chirenje, Chimbari & Chandiwana, 2006).

Another scholar, Lyimo & Beran (2012) noted that 59.6% of the 354 women aged 18 and 69 from Moshi-Tanzania had low knowledge about cervical cancer and its prevention. The same study indicated that only 12.6% women who had been screened were those with more knowledge about cervical cancer and its prevention.

Furthermore, a similar study conducted to assess the knowledge of cervical cancer among women in rural Nepal, explored the feasibility and impact of a community-based awareness program on cervical cancer. Community-based educational meetings on cervical cancer and its prevention were conducted among women's groups in rural Nepal. Using a questionnaire, the women's baseline knowledge of risk factors, symptoms and perceived risk of cervical cancer were identified. The willingness to participate in cervical cancer screening was compared before and after the educational meeting. The meetings were followed by a cervical cancer screening program. Among the 122 participants at the educational meeting, only 6 % had heard about cervical cancer. Their baseline knowledge of risk factors and symptoms was poor. However, the proportion of women willing to participate in cervical screening increased from 15.6 to 100 % after attending the educational meeting. All the study subjects participated in the screening program. The study participants recruited a further 222 of their peers for screening (Shakya et al, 2015).

Based on the above studies, it is logical to assert that inadequate knowledge about cervical cancer among women establishes the need for public awareness programs for cervical cancer at all levels within developing countries. Community-based awareness programs have presumed to be vital towards changing women's attitude to cervical screening and women peer groups can play a major role in promoting participation in cervical cancer screening programs.

2.6.2 Demographic features.

These include marital status, education and age. Several studies have found out that women who are educated are more likely to seek cervical cancer screening (Fernandaz et al, 2009). However, Abotchie &Sokar (2009) asserted that educated women may not necessarily seek screening. This implies that other relevant factors should be considered. Cyril, Esther,

Maduboko, Ngozi & Ezegwei (2009) asserted that screening uptake is essentially lower among women aged 20-29 and those aged 60 years and above. Similarly, Kahesa (2012) noted that screening acceptance was associated with being aged above 35 years, being married, having less than 5 children and having attended school. Were et al (2012) noted that women over 30 years were more likely to seek cervical cancer screening than younger women below 30 years.

2.6.3 Socio-economic factors

Poverty or low incomes among households is one of the major factors that have hindered effective up take of cervical cancer screening (Kahesa, 2012). According a study conducted in Eldoret at Moi Teaching and Referral Hospital 29.9 (11.4%) of the respondents asserted that lack of finances to pay for the screening impended them from accessing screening services. Furthermore, Twinomujuni et al (2015) noted that the distance to nearest screening centre ranged from 2km to 40km and only half of the 419 respondents lived within 20km from nearest screening centre. This implied that the transport costs to access screening services were relatively high ranged from Uganda shillings 3000 (equivalent to US$ 1.2) to 100,000 (equivalent to US$ 40) with an average cost of Uganda shillings 43,000 (equivalent to US$ 17.2). The total costs incurred for services were reportedly prohibitive for service utilization among 89.7% (174/194) of the respondents although this was not statistically significant (unadjusted PR 0.9, 95% CI 0.67–1.20).

This said situation has negative implications towards accessing screening services since 67% of Ugandans are either poor or highly vulnerable to poverty (The expenditure Review-Uganda, 2012, New Vision, 2013). Currently, Uganda has about 34.5 million people and about 23.1 million are prone to poverty, and about 8.4 million of them (about 24.5%) are trapped in absolute poverty. This implies that even though cervical screening is free, the associated costs to access are a high and many women are likely to miss it due to high transportation costs to screening centres.

Therefore, the improvement in the uptake of cervical cancer screening lies in developing a policy framework to remove these barriers so that the society can appreciate the advantages associated with early cervical cancer screening. Furthermore, this will form a basis to integrate cervical cancer screening into HIV care.

2.7 The Relationship Between Cervical Cancer and HIV/AIDS

On 1st January 1993, Centre for Disease Control and Prevention (CDC) expanded the surveillance case definition of AIDS to include HIV positive women with invasive cervical cancer (Maiman, Fruchter, Clark, Arrastia, Matthews & Gates, 1997, Adjorlolo-Johnson et al 2010). Since then AIDS case definition has included the development of cervical cancer in an HIV-infected person as a sufficient criterion for AIDS, even in the absence of an opportunistic infection (Adjorlolo-Johnson et al, 2010). Both HIV-1 and HPVs are sexually transmitted with no immediate visible symptoms and one of the two viruses may facilitate transmission of the other. This partly explains why the International Agency for Research on Cancer (IARC) has classified both human papillomavirus (HPV) and human immunodeficiency virus type 1 (HIV) as carcinogens: HPV is a direct carcinogen and HIV-1 is an indirect carcinogen through immune suppression. However, not all HPV-infected people will develop cancer, but it is only those with persistent HPV infection, specific HPV types, and high viral load that develop cervical cancer after some time (Williamson, 2015).

The role of HIV in the etiology of cervical cancer is unclear, especially in Africa where Immunosuppression is a risk factor for HPV infection. However, there is consistent evidence that HIV-positive women have higher prevalence of HPV infection and are more persistent infection that later result into higher rates of pre-invasive cervical lesions (Holmes et al, 2009). A woman's risk of developing cervical cancer is partly determined by her risk of having been exposed to HPV. The causal relationship between anogenital infections with specific high-risk types of HPV and cervical cancer may also explain the increasing infection of cervical cancer observed among women infected with HIV (Denny & Wright, 2009).

During the last two decades, the increased burden of cervical cancer has been exacerbated by the escalating HIV infections among women to cervical pre-cancer and cancer (Huchko, Maloba, Nakalembe & Cohen, 2015). Accordingly, this explains why Anderson, Enriquito Lu, Sanghvi, Kibwana &Anjanique Lu (2010) noted that areas where cervical cancer rates are highest usually have high prevalence of HIV of which the presence of HIV increases the risk of cervical precancerous and cancerous changes. This is very true for countries like Uganda and South Africa. For example, the incidence of cervical cancer is 42.7 per 100,000 women in Eastern Africa with a high HIV-prevalence region coupled with low screening coverage, compared to 30.6/100,000 in Middle Africa (moderate HIV prevalence, low screening) and 6.6/100,000 in Northern Africa (low HIV prevalence, moderate screening coverage).

Generally, immunosuppression and infection of HIV precisely pre-dispose to the advancement of cancer. Patients with AIDS have a higher risk of developing Kaposi sarcoma, primary central nervous system lymphoma and non- Hodgkin lymphoma 40,000, 3900, 191 times higher respectively than the entire populace (Maiman, et al, 1997). Thus, Immuno-compromised women are at increased risk for developing persistent HPV infections, which is a prerequisite for the development of cervical cancer precursors. The decrease in cellular immunity caused by HIV increases the risk for new and persistent human papillomavirus (HPV) infections (Huchko, Bukusi & Cohen, 2011).

HIV infected women are more likely to exhibit persistent HPV infection over time and this is associated with the development of invasive cervical cancer among women with HIV. Specifically, women infected with HIV-1 are more likely to be infected with multiple HPV types soon after HIV-1 infection compared with pre-infection. Thus, HIV type 1 is an extreme risk factor for HPV infection and the development of HPV- associated lesions in female genital tract (Fife et al 2006). This explains why Maiman (1997) asserted that the co-existence of HIV infection pre-invasive cervical cancer neoplasia is more common than that of HIV infection and invasive cancer. Although the development of AIDS-related malignancy is largely attributed to immunodeficiency, the relationship between cervical neoplasia and HIV is exclusive and is associated not only to immunosuppression but also to common sexual behavioural risk factors as well as the interactions between and HPV at molecular level. Several studies do indicate that correlation between HIV and cervical cancer is direct and deadly.

According to the study done in Cape Town on 1,371 HIV-positive women and 8,050 HIV-negative women, aged 17–65 years. The HPV prevalence was higher among HIV-positive women (52.4%) than among HIV-negative women (20.8%) in all age groups. HIV-positive women were more likely to have CIN 2 or 3 than HIV-negative women. Infections with multiple high-risk HPV types were more common in HIV-positive than HIV-negative women, controlling for age and cervical disease status (McDonald, Tergas, Kuhn, Denny & Wright, 2014).

Similarly, a meta-analysis relating to HPV type prevalence among HIV women in which 20 studies were selected, 5578 HIV positive women were identified mainly from North America and others from Africa, Asia and South Africa. From the study, 3230 had no cytological abnormalities; prevalence for any HPV was 36.3% and for multiple HPV was 11.9%. HPV16

was the most common type in 2053 HIV positive women with atypical squamous cells of undetermined significance of Low grade squamous intraepithelial lesion (LSIL) and High grade squamous intraepithelial lesions (HSIL). Women with HSIL were significantly more likely to be infected HPV16 than the general female population however HIV positive women with HSIL were extremely more inclined to be infected with HPV types 11, 18, 33,51,52, 53, 58 and 61 as well as multiple HPV types (Clifford, Goncalves & Franceschi, 2006).

Stein et al (2008) also noted that HIV-1 infection was associated with increased risk of cervical cancer in South Africa. A cross section study that was conducted in Senegal among sex workers and women at an outpatient clinic between 1994 and 1998 found that HIV was associated with increased rates of cervical cancer infection with high risk of HPVs. Those women with HIV plasma RNA loads and lower CD4 cell count were associated with high-risk HPV infection and degree of cervical abnormality and women with HIV-2 positive were more likely to have both HSIL and ICC with odds ratio of 3.7 and 6.7 respectively than those women with HIV-1.

Furthermore, Moodley, Moodley & Kleinschmidt (2001) carried out a study to compare the prevalence of invasive cervical cancer in women with and without HIV infection, to evaluate the inclusion of invasive cervical cancer in the AIDS surveillance case definition. The data on invasive cervical cancer obtained from medical record review and HIV serostatus from white, black, and Hispanic women in the age groups 20–34, 35–44, and 45–54 years was analysed from 14 hospitals with high HIV prevalence.

From the same study, out of 2684 (6.6%) of the 40,524 women sampled were HIV infected. Of the HIV-positive women, 28 had invasive cervical cancer (10.4 per 1000 women) and of the HIV-negative women, 236 had invasive cervical cancer (6.2 per 1000 women, relative risk [RR] 1.7, 95% confidence interval [CI] 1.1, 2.5). The prevalence of invasive cervical cancer was significantly higher within those women with HIV-positive than for HIV-negative black women aged 20–34 (RR 3.8; CI 1.7, 8.5) and Hispanic women aged 20–34 (RR 7.3; CI 1.4, 37.1) and 35–44 (RR 3.9; CI 1.1, 14.7) years. Twenty-six of the 28 cases of invasive cervical cancer in HIV-positive women were in women known to be HIV-positive during admission. Thus, the prevalence of invasive cervical cancer was higher for women who were HIV positive than for women who were HIV negative.

According to the study to measure the program effectiveness to implement cervical cancer prevention services for HIV-infected women in Zambia (Pahram et al, 2010). Between 2006 and 2008, 6572 HIV-infected women were screened, 53.6% (3523) had visible lesions, 58.5% (2062) were eligible for cryotherapy and 41.5% (1461) were referred for histologic evaluation. A total of 1095 out of 1462 (75%) of patients were referred evaluation. Pathology results from 65% 715 out of 1095 women (65%) of women revealed benign abnormalities in 151 (21%), CIN I in 214 (30%), CIN 2/3 in 235 women (33%) and invasive cervical cancer in 115 of which 69% were early stage (16.1%). A conditional probability model, indicated the program prevented 142 cervical cancer deaths (high/low range: 238-96) among the 6572 HIV-infected women screened, or one cervical cancer death prevented per 46 (corresponding range: 28-68) HIV-infected women screened. Thus, it can be fully asserted that the integration of cervical cancer into HIV care is a necessary strategy that would help to meet one of the various unmet needs of HIV positive women in developing countries. This explains why the Pahram et al (2010) noted that financial support was vital to enhance the integration of the two services.

MacLeod (2011) asserted that oncogenic HPV types are likely to prevalent in women with lower CD4 counts or those with higher viral loads. A CD4 count is a laboratory test that measures the number of CD4 T lymphocytes (CD4 cells) in a sample of your blood. It gives an indication of the health of one's immune system. The CD4 cell count of a person who does not have HIV is estimated to range 500 and 1500. Patients living with HIV who have a CD4 count over 500 are usually in good health. A very low CD4 count (less than 200 cells/mm^3) is one of the ways to determine whether a person living with HIV has progressed to stage three infections which is the AIDS defining stage (aidsmap, 2016; WHO, 2017). Therefore, among HIV patients, the use of CD4 is the most important laboratory indicator that reveals how well one's immune system is working and the strongest predictor of HIV progression. While HIV treatment is recommended for all people living with HIV but it is very important for people with low CD4 counts. However, in 2015 WHO issued new treatment guidelines for HIV/AIDS that recommend all those who test positive for HIV/AIDS to receive ART regardless of their CD4 count.

Furthermore, Palefsky, et al (1999) carried out cross-sectional analysis of cervicovaginal HPV infection using baseline data obtained from 1778 HIV-positive and 500 HIV-negative women. The study revealed that 1127 (63%) of 1778 HIV-positive women and 149 (30%) of 500

HIV-negative women were positive for HPV DNA. Women with the highest prevalence of HPV DNA were those with a CD4 level of less than 200/mm3, regardless of HIV viral load. At CD4 levels above 200/mm3, a higher prevalence of HPV DNA was found among women with an HIV viral load of greater than 20 000 copies/mL compared with those with an HIV viral load of less than 20 000 copies/mL. The lowest prevalence of HPV DNA was found among those women with a CD4 level above 500/mm3 and an HIV viral load of less than 4000 copies/mL. This research further demonstrated that cervical cancer is more prevalent in HIV positive women than their counter parts who are HIV negative as well as those with lower CD4 count.

Another study carried out in Johannesburg relating to diverse and high prevalence of HPV associated with a significant high rate of cervical dysplasia in human immunodeficiency virus-infected women in Johannesburg (Firnhaber et al, 2009). A cohort of 148 women with HIV-1 was studied, 54% had abnormal Pap smears, with 33% of these assessed as having high grade changes. HPV DNA was found in 95% of the 148 individuals assessed and 83% had 1 or more HPV oncogenic types. There was a significant risk of an oncogenic HPV type in women with CD4 < 200 cells/μL. In multivariate analysis, Jaquet et al (2012) noted that HIV-positive women with a CD4 count <200 cells mm^3 or between 200 and 499 cells mm^3 were more likely to harbour an oncogenic HPV compared with women with a CD4 count $\geqslant$500 cells mm^3 with OR of 2.8 (95% CI 1.1–8.1) and 1.7 (95% CI 1.0–2.9), respectively. This partly explains why scholars like Anderson et al (2010) noted that HIV women with lower CD4 count are more prone to cervical cancer.

These findings reveal why the integration of cervical cancer screening with HIV care is a necessary approach for countries like Uganda where the economic burden of both diseases is enormous. Thus, strategies for introducing or intensifying the integration of cervical cancer screening into HIV should focus on ensuring that appropriate and cost-effective screening services are provided to women. It is against this background that this study has been designed to investigate the cost effectiveness and clinical benefits of integrating cervical cancer screening into HIV care.

2.8 Feasibility, Effectiveness and Cost-effectiveness of Integrating Cervical Cancer Screening into HIV-care

Various studies have been conducted to assess whether the integration of cervical cancer screening into HIV care is feasible, effective and cost-effective in Sub-Saharan Africa. For instance, Plotkin et al (2014) asserted that the integration HIV care into cervical cancer screening was widely accepted by both the providers and the clients in Tanzania. However, the biggest challenge affecting the effectiveness of integration was insufficient supply of HIV test kits at the health facilities providing the service.

In Nigeria, a cross section study using a bi-directional referral between HIV and reproductive health (RH) services and provider initiated counselling and screening for cervical cancer indicated that integrating VIA screening into the package of care offered to HIV positive women is feasible and acceptable (Odafe, et al, 2013).

Furthermore, Kumakech et al, (2014) conducted a study relating to the Integration of HIV and cervical cancer screening perceptions of healthcare providers and policy makers in Uganda and one of the respondent noted that "It also reduces on the expenditure of the health system because instead of health workers going and making an outreach for HIV and making another outreach for cervical cancer screening, you have an opportunity to do both of them on the same client on the same day which is less expensive for the health system". Other benefits expressed by the respondents included reduction on the frequency of visits women would make to health facilities for healthcare services, travel time and cost saving to the women and their male partners, minimized loss to follow up of women scheduled for HIV and cervical cancer treatment, and correct or proper management of HIV positive women with cervical precancerous lesions. On the contrary, another respondent asserted that "The disadvantage of integration is that people associating cervical cancer screening with HIV testing. People may fear to come for the cervical cancer screening knowing that if you go to the screening, they will also test for HIV. There are some people who may fear"

Almost all the participants thought that integration will prevent HIV positive women on ARV drugs dying from cervical cancer however it was noted that in order for this initiative to offer lasting benefits it was imperative to address the existing weaknesses and inefficiencies in the health systems such as limited infrastructure, insufficient drugs and supplies, inadequate and poorly motivated healthcare workers.

A cost-effectiveness study of integrating cervical cancer screening and prevention into HIV-care in the Nyanza Province-Kenya (Huchko, 2012) compared a baseline policy of no cervical cancer screening with three strategies namely; Single Lifetime "See & Treat" with VIA and Cryotherapy, "See & Treat" every three years, Screen with VIA every three years with treatment for biopsy-confirmed precancer by LEEP.

The study revealed that screening with a single-lifetime "see & treat" visit with VIA and cryotherapy was the most cost effective compared to no treatment. The costs per cancer prevented ranged between $3400 - $4757, costs per cancer related death averted were between $4273 - $6111 and all the three strategies led to a gain in a QALY.

2.9 Summary of the Literature

Cervical cancer and HIV/AIDS do share similar risk factors. The economic burden of HIV/AIDS and cervical cancer is a very big public health concern. The integration of cervical cancer screening into HIV care remains one of the most appropriate mechanisms that will increase the uptake of cervical cancer screening among HIV positive women. Several studies have noted that the integration of these interventions is feasible and viable in Uganda however, the cost-effectiveness analysis of integrating cervical cancer into HIV-care needs to be determined in context to the country's resources.

Several studies indicate cervical cancer screening is the most effective and efficient mechanism of preventing cervical cancer. These studies note that, even if a woman were screened for cervical cancer only once in her lifetime between the ages of 30 and 40, her risk of cancer would be reduced by 25-36 % (Goldie et al 2005; Cervical Cancer Action, 2007). Cervical cancer can be prevented by identifying pre-cancerous lesions early using Pap smear, VIA and cytology screening and treat these lesions before they advance to cancer. Studies indicate that routine screening and treatment of high grade precancerous lesions has reduced mortality of cervical cancer in various developed countries as compared to developing countries.

3 AN OVERVIEW OF THE HEALTHCARE SYSTEM IN UGANDA

Preamble

The social-economic set up of the country has serious consequences on the accessibility and utilization of the available healthcare facilities. This chapter gives an insight on the social-economic structure of Uganda, the structure of the country's healthcare system and policy strategy behind it, how the healthcare sector is financed, how the general population accesses healthcare services and the challenges faced by the entire healthcare system amidst the growing economic burden of disease.

3.1 The Social-economic Status of Uganda

The Republic of Uganda is a landlocked country found in East Africa, north of Lake Victoria with neighbours Kenya, Tanzania, Rwanda, Burundi and South Sudan. Uganda was colonized by Britain and gained independence in 1962 (Swecare Foundation, 2013). The country is estimated to have a total population of 36.9 million with an average population growth rate of 3%. The population is projected to be 47.4 million in 2025 (Uganda Bureau of Statistics, 2014). The life expectancy of Ugandans increased to 59 years in 2013, from 54.8 years in 2010. The total fertility rate is approximately 6.2 births per woman, 88% of the population live in rural areas, 48.5% of the population are male while 49% of the population are persons under the age of 15 years and 18.5% are under 5 years (WHO, 2014).

According, to the Africa Development Indicators (2008/09) the unemployment among the young people aged 15 to 24 was estimated to be 83 per cent. The report also noted that country has the highest dependency ratio in Africa registered at 1:1 (Dependency ratio is the ratio of people younger than 15 or older than 64 to the working age population). Uganda has one of the youngest populations in the world.

During the financial year 2014/15, GDP at constant prices was estimated to grow by 5.0%. However, the increasing population growth rate is one the factors that has hindered economic growth in real terms. According to the Uganda Bureau of Statistics (2015), 19.7% of Ugandans are poor, these account to 6.7 million people. The poor in the rural areas represent 22.8% of the population compared to only 9.3% in the urban areas. The rural population accounts to 77.4% of the entire population and this constitutes of 89.3% of national poverty.

On the other hand, the urban areas represent 22.6% of the entire population and constitutes 10.7% of national poverty (UBOS, 2015).

Uganda is a low-income nation whose GDP at market prices is estimated to be $ 27 billion (World Bank, 2014) and the GDP per capita is 686 USD (Swecare Foundation, 2013).

Increasing poverty, high population growth rate and escalating youth unemployment are the major social-economic challenges that have undermined economic growth and development in Uganda.

3.2 Structure of the Healthcare System

The entire healthcare sector is managed by the Ministry of Health through a decentralised system. This system has yielded mixed outcomes are far as the utilization of healthcare services is concerned. Anokbonggo, Ogwal-Okeng, Obua, Aupont, Ross-Degnan (2004) noted that the decentralization policy led to increased utilization of healthcare facilities and since then it has empowered the communities in terms of creating a sense of responsibility in the stakeholders, and a sense of ownership that facilitated sustainability.

The major healthcare providers include public hospitals, private-not-for-profit, and private-for-profit as well as complementary and traditional practitioners. Health facilities include hospitals and health centres (II, III and IV) and these sum to about 5,229 healthcare facilities. Government hospitals (2,867) comprise of health centre II, III and IV. At the district level, we have health centres (II-IV) and these are correspondingly found at village, parish, sub-county and county level. All these report to the local government within the district (Zikusooka, Kwesiga, Lagony & Abewe, 2014). Health Centres II provide the first level of interaction between the formal health sector and communities, provide only out-patient care, community outreach services, and linkages with the VHTs. HCIIIs provide basic preventive, promotive, and curative care as well as supportive supervision of the community. General hospitals and regional referral report to the central government.

Private-not-for-profit (874) hospitals are mainly governed by the respective bureaus or various religious institutions. These comprise of clinics and during the last decade some have grown into providers of specialised care (Zikusooka et al, 2014; UBOS, 2015). At least 75% of the facility-based PNFP organisations exist under four umbrella organisations namely; The Uganda Catholic Medical Bureau (UCMB), the Uganda Protestant Medical Bureau (UPMB),

the Uganda Orthodox Medical Bureau (UOMB) and the Uganda Muslim Medical Bureau (UMMB). In the field of TCMPs, there is recent emergence of non-indigenous traditional or complimentary practitioners such as the practitioners of Chinese and Ayurvedic medicine (The Second National Health Policy, 2010)

Private-for-profit healthcare facilities add up to 1488 and these almost double private-not-for-profit healthcare facilities (UBOS, 2015). This shows that the provision of healthcare facilities in Uganda is largely driven by profit (Zikusooka et al, 2014). This has made the access of healthcare extremely expensive especially during the era when the economic burden of communicable and incommunicable diseases is tremendously increasing. It is worth noting that the prices of medical care are privately determined within the private-for-profit.

Even though more than 75% of the total population resides in rural areas however, majority of the health care centres are in urban areas. For instance, more than a quarter of the health facilities are found in Kampala (capital city). Kampala also has the highest number of private health facilities and four other districts have more than 100 health facilities and these include Wakiso, Jinja, Kabale and Kasese (UBOS, 2015). This reveals the uneven distribution of healthcare centers in Uganda.

3.3 Health Policy and Strategy

Constitutionally, the Government of Uganda (GoU) has a commitment to provide basic health services to its people. The 1995 Constitution of the Republic of Uganda (as amended) further provided for all people in Uganda to enjoy equal rights and opportunities, have access to health services, clean and safe water and education, among many other things. Investing in the promotion of people's health and nutrition ensures that the population remains productive and contributes to national development (The Second National Health Policy, 2010).

It is against this background that the goals of the Ministry of Health include; reducing morbidity and mortality from the major causes of disabilities and inequalities through delivery of essential healthcare package and improving access to quality hospital services at all levels in both the public and private sectors. This entails the reduction of the disease burden of both communicable and non-communicable diseases, maternal and childhood illness through a Sector Wide Approach (SWAp) by mobilising funding, improve efficiency, recruitment and deployment of health workers in rural areas, improvement of the infrastructure, distribution and access to drugs (Okwero, Tandon, Sparkes, Mc Laughlin & Hoogeven, 2010).

The accomplishment of the above goals requires the MoH to carry out these policy strategies; resource mobilisation and budgeting; policy formulation and policy dialogue with Health Development Partners, strategic planning, regulation, advising other ministries on health matters, setting standards and quality assurance, capacity development and technical support, provision of nationally coordinated services such as epidemic control, co-ordination of health research, monitoring and evaluation of the overall sector performance, strengthening the development of specialised hospital such as Uganda Heart and Uganda Cancer Institutes and providing services in an integrated manner to enhance harness efficiency (The Second National Health Policy, 2010).

The National Health Policy focuses on health promotion, disease prevention and early diagnosis and treatment of disease with emphasis on vulnerable populations such as the elderly. It further entails developing cost effective interventions at primary, secondary and tertiary preventive levels. Specifically, this is to be achieved through the establishment of a functional integration within the public and between the public and private sectors in the delivery of healthcare services, training and research; strengthening health systems in line with decentralisation through training, mentoring, technical assistance and financial support among others.

Therefore, the development of cost-effective interventions is the policy mechanism for healthcare service delivery in Uganda.

3.4 Healthcare Financing in Uganda

This entails resource mobilization, pooling, allocation and utilization of resources to ensure that best and equitable health care services are received to the population. Healthcare financing is an essential part in the process of shaping national healthcare systems and strategies towards achieving universal coverage and social health protection especially for the most vulnerable individuals such as the elderly. The major healthcare funding is mainly derived from the GDP allocations (German Foundation for World Population, 2010). The sources of healthcare finances in Uganda include taxes; direct and indirect and these account for roughly one-third and two-thirds of taxes respectively, hefty amount of out-of-pocket payments, substantial donor funding and minimal voluntary health insurance (through private insurance and community based insurance).

During the last eight years, the total expenditure on health as a percentage of GDP has been estimated to be 9.76% (World Bank, 2013; The Second Health Policy, 2010). It covers the provision of health services (preventive and curative), family planning activities, nutrition activities, and emergency aid designated for health but does not include provision of water and sanitation. This translates into only 1.9% of GDP. However, the healthcare expenditure as a proportional of GDP is far below the country's commitment in Abuja Declaration of 2001 where African countries pledged to allocate at least 15% of their annual budget to improve the health sector. By 2011, only Rwanda and South Africa had achieved the Abuja Declaration target of "at least 15%" (WHO, 2011).

External funds (from development partners and global health initiatives) are channelled through general budget support and through projects (on- and off-budget). Most of the public health budget (85%) is in the form of earmarked funding for specific programmes or health facilities. This not only limits the flexibility needed in resource allocation but also leads to budgetary distortions (Okwero et al. 2010). The allocation of resources from development assistance for donor projects, especially the off-budget support, is not very transparent and is usually based on interventions for specific diseases. In some instances, allocation of external resources is not always in line with core government priorities (Zikusooka et al, 2014).

The low government expenditure towards the healthcare sector implies the access and quality of healthcare is limited amidst a high the burden of communicable and Non-Communicable Diseases. Moreover, to deliver the minimum healthcare package, the health sector needs an estimated USD 40 per capita. However, during the last years the total public allocation to health per capita has been USD 10.40, which is still largely insufficient to meet the population's needs amidst the increasing burden of disease (Health Spending in Uganda, 2010).

3.5 Access to Healthcare Services in Uganda

Health care access is defined as the opportunity or ease with which consumers or communities can use appropriate services in proportion to their needs. Access has been defined as the use of health care, qualified by need for care and describes the costs incurred in receiving care, as the maximum attainable consumption, or as foregone utility (Levesque, Harris & Russell, 2013).

The access to healthcare includes the following aspects namely; how are the healthcare services delivered, how much Ugandans pay to access healthcare, what the healthcare package includes, how long it takes for one to access healthcare, what the quality of the service is and who it is that is responsible to provide and assess the quality of the care.

The MoH has a mandate to ensure that all Ugandans access a minimum health care package which consists of the most cost-effective priority healthcare interventions which address the high disease burden. This should be acceptable and affordable within the total resource envelope of the sector. The Second National Health Policy (2010) states that the package shall consist of the following clusters;

(a) Health promotion, environmental health, disease prevention and community health initiatives, including epidemic and disaster preparedness and response

(b) Maternal and Child Health;

(c) Prevention, management and control of communicable diseases

(d) Prevention, management and control of non-communicable diseases. At what cost and convince do Ugandans get access to this minimum health care package?

In 2001, the government abolished the user fees in public hospitals, this type of payment excluded vulnerable populations from access to health services and placed them at risk of further impoverishment. Soon after its abolition the public health care utilisation particularly among the poor increased on the contrary among the rich, utilisation decreased to a rate even lower than before the elimination of these fees (Kwesiga, Zikusooka & Ataguba, 2015). This was attributed to the variations in quality which has continued to occur.

The access for healthcare in the private sector (including the private wings of public sector hospitals) is based on a fee-for-service basis often through out-of-pocket payments. This has escalated healthcare cost within the entire sector. Several studies do reveal that the private health sector is the preferred provider for both the rich and the poor in Uganda. This implies that low income households continue to incur a catastrophic out of pocket payment to access healthcare from private providers whose quality is assumed to be better than public hospitals (Zikusooka, et al, 2014). Another factor that has attributed to the high out-of-pocket payments is the presence of informal payments in the public health facilities.

The WHO definition of catastrophic health expenditures contends that health expenditure should be called catastrophic whenever it is greater than or equal to 40% of the household's non-subsistence expenditure (Orem et al, 2013). Kwesiga et al (2013) noted that the out-of-pocket payments as a percentage of private health expenditure in Uganda increased from 56.7% in 2000 to 64.8% in 2011. The most recent national health accounts exercise indicated that household contribution through out-of-pocket payments is the dominant source of health expenditure. During the fiscal year 2009/10, out-pocket payments contributed to about 50% of the entire healthcare expenditure. Thus, majority of the household face a catastrophic out-of-pocket payment to access health care services.

This has a negative impact on the household welfare and has led to impoverishment; this is because about 66% of the total households do live on less than 2.5 USD per day and when out-of-pocket expenditures on health care are considered, about 4% of the population is likely to be impoverished, which represents 17.5% relative rise in poverty which indicates that 1.4 million Ugandans are likely to be poverty-stricken (Zikusooka et al, 2014).

Private insurance contributes to less than 1% of the total health expenditure, but with a growing formal labour market, private insurance providers are also increasing rapidly. Private voluntary health insurance represents over 20 small risk-pools in the form of small and highly fragmented community-based and commercial health insurance schemes. Private insurance packages are dependent on the individual's level of contribution and these vary widely.

The distance an individual should travel to access health care services usually has a bearing on one's preference of the type of health care source utilized. The Uganda National Household Survey Report (2009/2010) indicated that almost a half of the population that falls sick seeks treatment from private clinics within 5 Km.

Much as the objective of universal health coverage is to provide financial protection for everyone in the country, the current catastrophic health expenditures, the absence of a National Health Insurance indicate, the price competition among healthcare providers, poor monitoring and regulation of the private sector and the informal payments in public hospitals indicate that the access to care in Uganda is completely contingent on one's ability to pay. This indicates that healthcare is denied to those who need most (poorest) yet several medical studies have revealed that the poorest are also the sickest, independent of access to care (El-sayed, 2012). On the contrary, the country is facing an epidemiological transition in global

health from infectious diseases to NCDs which is posing not only a threat to the health of those affected but also places an enormous burden on the health systems and families who incur huge amount money to access quality health.

3.6 General Challenges Facing the Healthcare Sector in Uganda

From the above discussion, it is eminently clear that the healthcare faces several significant challenges namely but not limited to;

The inadequate manpower resource is one of the devastating factors affecting the healthcare sector. Statistics indicate the doctor-patient ratio is 1:24,725 while other reports indicate a ratio of 1: 35,000 of the total population and on the contrary WHO recommends one doctor for every 1000 patients (Ladu, 2015).

At least 50% of the healthcare budget is funded by donors such as United States Agency for International Development (USAID), United Nations Children's Fund (UNICEF), UNAIDS and the World Bank (Ladu, 2015). This implies that they dictate the specific areas where the given funds should be spent. During the last decade, these organisations have bent a lot of their efforts to fight communicable diseases like malaria, HIV/AIDS, Tuberculosis among others on the contrary the burden of NCDs has greatly increased yet the budgetary allocations have remained low. This partly explains why the treatment and management of NCDs such as cervical cancer has remained very expensive in Uganda.

Access to healthcare should be based on the need for health services rather than one's inability to pay. However, the increasing out-of-pocket payments have threatened the households' livelihoods and access to healthcare especially among those suffering from NCBs (Zikusooka, Tumwine&Tutembe, 2009). This explains why scholars such as Zikusooka et al, 2014) have greatly recommended that the current bill of the National Healthcare Insurance be enacted into law to protect households from impoverishment.

In summary, underfunding of the healthcare and wastage of the healthcare resources are the root causes of the pending healthcare problems such as inadequate human resources, low morale among healthcare workers, poor infrastructure and among others. All these have hindered the effective management of both NCDs and communicable diseases.

4 DATA COLLECTION AND METHODS

Preamble

This chapter explains the various methods of data collection that were used to analyze the primary and the secondary objectives of the study.

4.1 Description of the Study Site

Mildmay Uganda

Mildmay Uganda formerly known as Mildmay International, is a national Non-Government Organization that was established in Uganda in 1998 as a Centre of Excellence for provision of comprehensive HIV/AIDS prevention, care, treatment and training services.

Since its establishment, Mildmay-Uganda has become a prominent centre that provides specialised HIV care such as treatment, health system strengthening and health training education and research. Currently, its services are being offered in 16 districts with support The U.S. President's Emergency Plan for AIDS Relief (PEPFAR) through CDC and it is expanding. It is accredited as a centre for higher learning by the National Council of Higher Education (NCHE) (Mildmay-Uganda, 2012).

Mildmay-Uganda also provides Paediatric Palliative Care Training as well as focusing towards empowering young people living with HIV&AIDS to make healthy sexual and reproductive choices. This partly explains why Mildmay-Uganda is one of the few centres that provide cervical cancer screening to HIV positive women.

Much as this centre is one of the leading providers of HIV care with cervical cancer screening, the CEA of this intervention has not yet been carried out. Mildmay Uganda provides cervical cancer screening using VIA and only provides cryotherapy which treats only pre-cancer but refer those patients who need LEEP and biopsy to referral hospitals like Nsambya and Mulago or any other referral hospital.

4.2 Study Subjects

Patients eligible for the study included all women consecutively diagnosed with HIV/AIDS at Mildmay-Uganda who had received cervical cancer screening January 2012 to August 2016.

4.2.1 Inclusion criteria:

- Ugandan citizens

- HIV positive women

-Age 25 to 64 years

4.2.2 Exclusion criteria

- Incident cases of whose who had already undergone primary treatment for cervical cancer

-Non-Ugandans.

- Those aged less than 25 or more than 64 years.

-Those who had received cervical cancer beyond August.

-Those who had never received cervical cancer screening by August 2016.

4.1 Data Sources, Collection Methods and Collection Tools

Cost data and the data relating to the utilization of cervical cancer screening were collected from January to August 2016 using questionnaire designed to ask the healthcare providers various questions that gave an insight on how the respective health care facility conducts cervical cancer screening and the costs incurred from the provider perspective and the challenges they encountered. This questionnaire was answered by the respective heads of the cervical cancer screening and procurement at Mildmay-Uganda. This intended to provide insights into utilization and cost-effectiveness of integrating cervical cancer screening into HIV and AIDS care and cost relationships with demographic characteristics, access to care, and quality and formulate strategies to improve the integration of cervical cancer screening into HIV care in Uganda.

4.2 Target Population

By using the RCR, 16,366 patient folders were reviewed at Mildmay-Uganda and 2,065 met the criteria of the study. This signified 12.6% of the total number of HIV/AIDS patients who had been enrolled for HIV/AIDS treatment at Mildmay-Uganda from 2012 to 2016.

4.3 Description of the Intervention

Counsellors and healthcare workers at Mildmay-Uganda fully understand that HIV positive women have a higher risk to get cervical cancer compared to their counterparts who HIV negative. They frequently encourage them to receive routine cervical cancer screening every after one year.

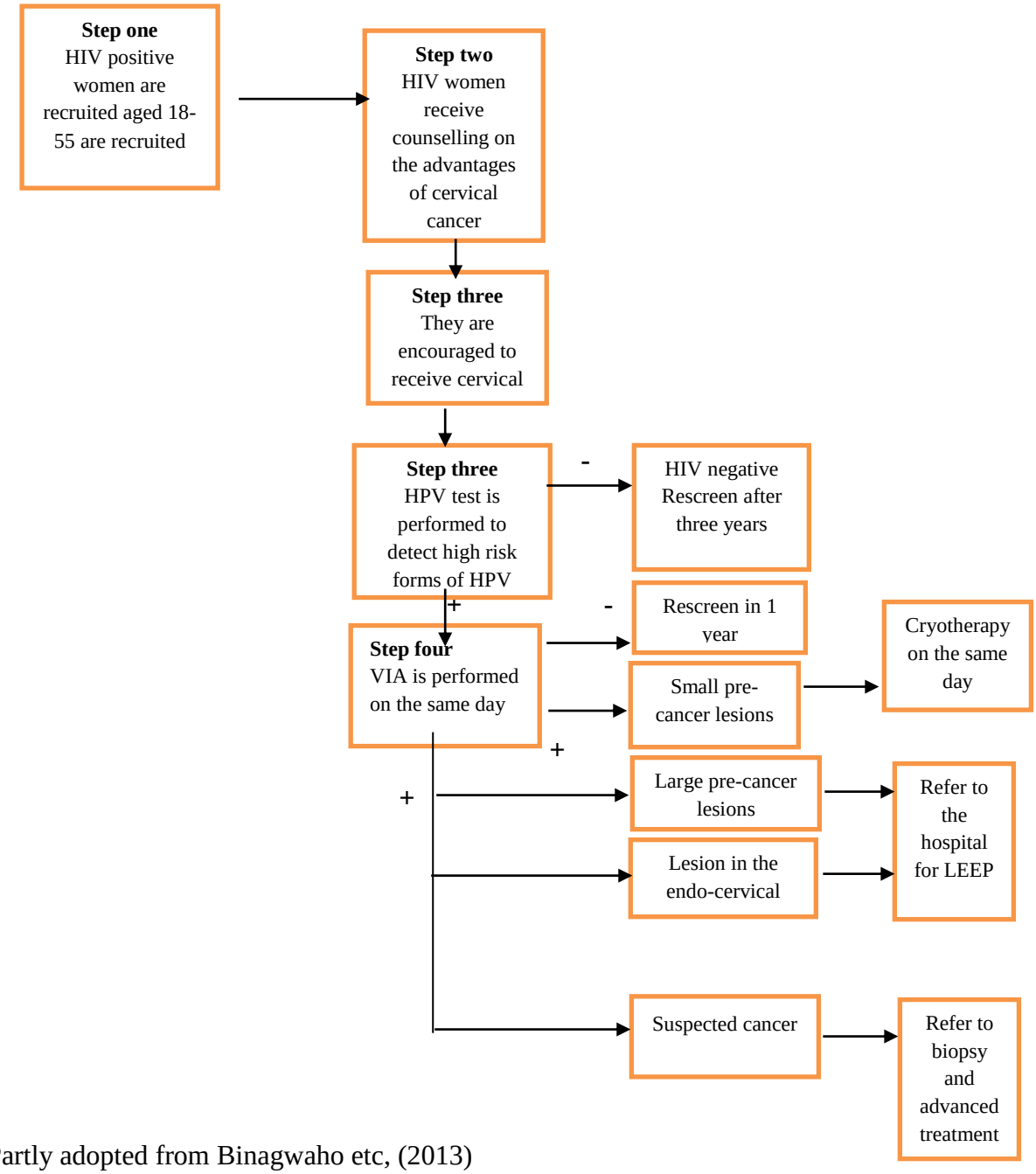
Just like other screening centres, Mildmay-Uganda uses VIA with acetic acid (3% to 5%) of a white table vinegar solution. These items are used to conduct the screening namely; a report form or register to record the result, an examination table that enables the woman to position herself so that the clinician can insert a speculum and view the cervix, adequate light source (halogen torch or flashlight), instrument tray, cotton swabs, vaginal speculum that can be locked open, leaving the examiner's hands free to adjust the light and swab the cervix, new examination gloves or high-level disinfected surgical gloves.

Based on the observed signs the health worker categorised VIA test results as summarised in the table below.

Table 4.1: Classification of test results using VIA

Test Negative	**Test positive**
No acetowhite lesions, faint acetowhite, polyp, cervicitis, inflammation, nabothian cysts	A sharp, distinct, well-defined, dense (opaque/ dull oyster white acetowhite areas with or without raised margins touching the sqamocolumnar junction, leukoplakia and warts.

Figure 1: Clinical pathway for cervical cancer screening



Partly adopted from Binagwaho etc, (2013)

4.4 Research Design

The methodology that guided the study was a retrospective chart review (RCR), also known as a medical record review. The retrospective chart review (RCR), also known as a medical record review will be used. Patient data that was collected exited in both soft and hard copies. This is a type of research design in which pre-recorded, patient-centred data are used to answer one or more research questions. The data used in such reviews exists in many forms: electronic databases, results from diagnostic tests, and notes from health service providers to mention a few. RCR is a popular methodology widely applied in many healthcare-based disciplines such as epidemiology, quality assessment, professional education and residency training, inpatient care, and clinical research (Matt & Matthew, 2013).

The RCR helped to answer questions like; what the prevalence and incidence of cervical cancer among HIV positive patients is; which age bracket is mainly affected with cervical cancer; what the type of cervical cancer dysplasia based on the classification system of CIN is, among others. A series of research questions were formulated prior to the initiation of study and these were used to review medical records of the HIV patients who had received cervical cancer screening from these centres. A pilot study was conducted and healthcare workers responsible for screening were asked to state the various items used for cervical cancer screening and treatment using cryotherapy.

Factors that influence a positive cervical cancer result

The first objective of the study was to identify factors associated with positive screening result. The independent variables considered are age of the woman, CD4 count at time of screening and their ART status at time of screening.

Table 4.2: Description of variables and their measurements

Variable Name	Description	Coding	Data type/ scale
Cervical Cancer test result	Result of VIA cervical cancer test screening	1. Negative 2. Positive	Nominal
Age	HIV positive woman's age at time of screening	1. 20-29 2. 30-39 3. 40-49 4. 50 and above	Nominal
ART status	HIV positive woman's ART status at time of screening	1-ART Naive 2- On ART	Nominal
CD4 count	HIV positive woman's CD4 count at time of screening	1-Less than 200 2-200-500 3- More than 500	Nominal

Data Management

Data was in excel format that was exported to STATA 13 for cleaning and analysis.

Data Analysis

The analysis was done at the following stages. First, in the analysis, an assessment of frequency distribution of the dependent (cervical cancer) and independent variables (age, ART status and CD4 count) were made using descriptive frequency tables and then associations were investigated using the Pearson Chi-square test. Multivariable associations were studied by logistic regression.

Associations between the variables were established at 5% and 1% levels of significance.

4.5 Estimating the costs of the intervention

Regardless of the results obtained from screening activity various costs are incurred to conduct this intervention.

Costs were estimated from a provider perspective. Only institutional costs incurred by Mildmay-Uganda were included in the study. The procurement and the finance departments were contacted to provide the unit cost of the various items that are used in conducting cervical cancer screening. Similarly, the nurses who conduct cervical cancer screening were contacted to provide the utilization period of these items. It was noted that that 16-25 women are screened per day. A conservative approach was used and 16 women were used to calculate the cost of screening one HIV positive woman. Cervical cancer screening costs included the cost of supplies per patient for VIA and the salaries of nurses and the program costs such as training. Items such as kidney bins, bed linen, curtains and curtain stand, disposing bin were assumed to last for only one year thus so no depreciation was involved.

Information relating to staff salaries was provided by the Mildmay-Uganda Accounting Department. Consultation with the screening team was done to determine the time spent to screen one HIV positive woman. Using this data, we calculated the average monetary cost of staff time allocated to cervical cancer screening and cryotherapy as the only form of treatment used at the point of screening to treat precancer lesions CIN II. Screening and cryotherapy were assumed to last 30 minutes and 15 minutes respectively.

The cost for cryotherapy was calculated by adding medical personnel cost (salaries and wages as a fraction time spent to offer cryotherapy) and cost of supplies and equipment for used to offer cryotherapy. All costs were converted from Ugandan shillings to US dollars (US $1 = 3600 shillings) using the currency exchange rate for the year 2016. The following costs of screening intervention were involved in the analysis;

- Screening costs and health outcomes per person screened
- Program costs e.g. costs of screening kits, costs of diagnostic and pathology tests
- Screening results e.g. test negative and positive; and

• Overall outcomes in terms of Health Care cost savings and life years gained from mandatory screening against life years gained from voluntary cervical cancer screening of HIV positive women.

The total cost of screening for cervical cancer among who had voluntarily received cervical screening and those who were detected positive for cryotherapy was estimated. This was subtracted from the cost of screening the entire population using the formulas below.

4.5.1 Cost of cervical cancer among women observed in the data (status quo)

= (N1 * C1*N2 * C2) where

N1 = Total no. of HIV positive women screened at MildMay-Uganda in 2012-2016

C1 = Cost of screening one woman

N2 = Total number women who were treated with cryotherapy from 2012-2016

C2 = Cost of cryotherapy

4.5.2 Cost of cervical screening if all women from 2012 to 2016 at Mildmay-Uganda were to be screened

= (N1 * C1) + (N1 * P2 * P * C2)

N1 = Total no. of HIV positive women at MildMay-Uganda in 2012-2016

C1 = Cost of screening one HIV positive woman

C2 = Cost of cryotherapy

P2 = Probability of being treated with cryotherapy after a positive cervical cancer result

P = Proportional of women treated with cryotherapy to those who screened

4.6 Defining and measuring health effects

Several studies have indicated a higher prevalence of cervical intraepithelial neoplasia (CIN) among HIV-positive women than among HIV-negative women. Even though ART reduces the risk of progression to cervical cancer in women with cervical abnormalities only modestly, the progression of cervical cancer is eight times more likely in women with HIV infection. However, cervical cancer can be prevented through early screening by identifying and treating precancerous lesions. CIN I spontaneously regress however if untreated, CIN II - III has a high probability of progressing to squamous cell cancer, and has a high probability of progressing to cervical cancer if not detected and treated early (Odendal, 2011).

In low resource setting economies, using VIA and treatment pre-cancer lesions (CIN II) using cryotherapy on the same day has been regarded as a cost-effective measure by WHO. This implies that routine screening and treatment of pre-cancer lesions using cryotherapy is the best option to mitigate the risk of developing cervical cancer among high risk HIV positive women. Women who are treated with cryotherapy are likely to gain an additional number of life years from this intervention thereby increasing their life expectancy which would be comparable to those who are negative.

Mills (2011) noted that life expectancy of HIV positive women on ART aged 35 years was 22 years thus summing up to 57 years. This is comparable to the life expectancy of HIV negative women whose life expectancy is 58.6 years (UNDP, 2016). Therefore, the study measured the number of life years an HIV positive woman gains from seeking early cervical screening or treatment of precancer lesions (CIN II) using cryotherapy that may later develop into invasive cancer. The total number of life-years gained if all HIV positive women in study were screened was estimated and subtracted from life-years gained from HIV positive women who voluntarily received cervical cancer screening and treated with cryotherapy as a form of treatment for those with CIN II. The formulas below were used to estimate the life years gained from screening

4.6.1 Life-years gained under screen all strategy

= N1*P1*P2*(Age1-Age2) where

N1=Total no. of women in population

P1=Probability of a positive cervical cancer result

P2=Probability of being treated with cryotherapy after a positive cc result

Age1=Life expectancy HIV Positive women in Uganda

Age2=average age HIV positive women in the sample

4.6.2 Life years gained from the status quo

N2*(Age1 - Age2) + (N1 * P2 * N2/ N3 – N2) * (P3*(Age1- Age2) + (1-P3) *2.5) where

N1=Total no. of women in the population

N2 = Total number women who were treated with cryotherapy from 2012-2016

Age = Age1=Life expectancy HIV Positive women in Uganda

Age2 = Age2=average age HIV positive women in the sample

N3 = Total number of HIV positive women with a positive cervical cancer screening result

P2=Probability of being treated with cryotherapy after a positive cervical cancer result

P3 = Probability of developing stage one of cervical cancer among women was 0.83 if CIN goes undetected

The formulas for estimating life-years gained from screening under both scenarios is based on the following assumptions.

1) The study assumed that the life expectancy of HIV positive women on ART was 58.65 (Mills, 2011)

2) Using a 5-five-year survival probability analysis, Nelson, Kim, Wilson, Soliman, Ngoma, Kahesa& Mwaiselage (2016) estimated that women have 0.83 chances of developing stage one of cervical cancer if CIN is undetected so since several studies from the literature do indicate that HIV positive women are two to eight times more likely to develop cervical cancer compared to their counterparts who HIV negative. This study assumed that the probability of developing stage one of cervical cancer if CIN was undetected 0.83.

4.7 Cost-Effectiveness Analysis

An incremental cost-effectiveness ratio (ICER) was calculated by dividing the differences in total costs by the difference in life-years gained. Finally, Gross Domestic Product (GDP) per capita for Uganda (2014) was used to determine the cost-effectiveness of the screening programme. According to the International Monetary Fund (IMF) and World Economic Outlook (WEO) database (2014) Uganda's GDP per capita was estimated to be 686.8 USD.

4.8 Sensitivity Analysis

Sensitivity analysis was conducted to assess the uncertainty about the model parameters, affects the estimation of costs, health outcomes and the robustness of the results of the economic evaluation. Almost all parameters used in the model were estimates; there was uncertainty surrounding their true values. The purpose of sensitivity analyses was to capture this uncertainty in the model (Haute Autorité de santé, 2012). A probabilistic sensitivity analysis was preferred because it incorporates uncertainty about all the parameters of the model, considering interactions. It allows correct estimation of the expected value of costs, health outcomes and provides useful information for constructing plotting a cost-effectiveness plane, a Cost-Effectiveness Acceptability Curve (CEAC). The CEAC is derived from the joint distribution of incremental costs and incremental effects. Thus, CEAC summarized the uncertainty in estimates of cost-effectiveness. The CEAC, derived from the joint distribution of costs and effects, illustrates the (Bayesian) probability that the data are consistent with a true cost-effectiveness ratio falling below a specified ceiling ratio (Fenwick, Marshall, Levy & Nichol, 2006). The main results were then re-calculated 1000 times; each time all the model parameters were set simultaneously, selecting from the respective parameter distribution at random.

The incremental cost and incremental effect were represented using the incremental cost-effectiveness plane. This shows the spread of pairs of incremental costs (ΔC) and incremental effectiveness (ΔE) values by running 1,000 Monte Carlo simulations. The incremental effectiveness was presented on the x-axis against incremental cost on the y-axis, such that the slope of the line joining any point on the plane to the origin is equal to the incremental cost-effectiveness ratio (ICER). In the Monte Carlo simulations, the differences in costs (ΔC) and effectiveness (ΔE) between the two interventions were used as base-case point estimates Fenwick, Marshall, Levy & Nichol, 2006; Cohen & Reynolds, 2008).

The horizontal axis divides the plane according to incremental cost (positive above, negative below) and the vertical axis divides the plane according to incremental effect (positive to the right, negative to the left). This divides the incremental cost-effectiveness plane into four quadrants through the origin. If the ICER for the screening all

If the ICER of the new intervention (screening all) fell in the northeast quadrant then the intervention is more effective and more costly and increases health effects. However, if the ICER of the new intervention fell in the northwest quadrant then the intervention is less effective and more costly and decreases health effects (Fenwick, Marshall, Levy & Nichol, 2006).

Similarly, if the ICER fell in the southwest quadrant, then the intervention is less effective and less costly. Finally, if the ICER of the new intervention fell in the southeast then the new intervention is more effective and most costly.

Under sensitivity analysis, the parameters of the model were evaluated for the expected outcomes under different scenarios. The cost of screening and that of cryotherapy varied between the lowest cost incurred under when screening maximum and minimum number of women reported in the study. The survival probability varied between plus or minus 10%.

5 RESEARCH FINDINGS OF THE STUDY

5.1 Description of the screening patterns

The table below shows the screening patterns from 2012 to 2016. The year 2012 had the highest detection rate. The average age of the patients was 35.5 years.

Table.5.1: Table showing screening patterns by year

Year	Number of HIV positive women	Number of Screened women	Number of CC positive women	Those who received cryotherapy	Probabilities of positive cervical cancer screening
2012	1510	168	25	5	0.029
2013	5734	344	32	8	0.023
2014	1122	356	29	11	0.031
2015	435	392	16	4	0.01
2016	7565	805	11	5	0.007
SUM	16,366	2,065	113	33	0.0159

The table above indicates that from 2012-2016, 16, 336 women received HIV/AIDS care at Mildmay-Uganda. From the 2,065 HIV, positive women voluntarily tested for cervical cancer and 113 tested positive for cervical cancer from and 33 were liable to receive cryotherapy. The probability of a positive cervical cancer result was 0.055 (P1) and the probability of being treated with cryotherapy was 0.0159 (P2).

The 2,065 patients who screened for cervical cancer had the following patient's characteristics. These are based on age, CD4 count and ART status.

Patient characteristics

This presents a descriptive summary of age, cd4 count, ART status patient characteristics.

Table 5.2: Distribution of patient characteristics

Characteristics		n=2,065	Percentage (%)
Age			
	Below 30	534	25.9
	30-39	903	43.7
	40-49	523	25.3
	50 and above	105	5.1
ART status			
	ART Naïve	172	8.3
	On ART	1893	91.7
CD4 count			
	Below 200	330	16.0
	200-500	932	45.1
	500 and Above	803	38.9
Cervical cancer screening result			
	Positive	113	5.7
	Negative	1952	94.5

The results from Table 5.2 indicated that the highest percentage of HIV positive women were aged between 30 to 39 years. More so, majority of the patients were on ART (91.7%) and 94.5% of these had a negative result.

5.2 The relationship between cervical cancer and age, treatment and CD4

Results from the Binomial Logistic Regression (BLR)

The results are presented in three major stages. First, an analysis of patient's age, CD4 count, art status, and cervical cancer screening results is presented using frequency distributions. Second, an assessment of the association between cervical cancer screening results and age, CD4 count, art status, is made using a chi-square test and fisher's test as deemed necessary. Third, all independent variables incorporated at the bivariate stage were investigated further at

the multivariate stage using a binomial logistic regression. The subsequent sections present a detail of the analysis and results based on these three stages.

Associations of Cervical cancer screening result and independent variables

Table 5.3, presents an assessment of associations between independent variables and the dependent variable. The analysis was made using the Log-Rank Chi-square test/Fishers exact test.

Table 5.3: Associations of cervical cancer screening results

	Cervical cancer screening result			
Characteristics	**Negative n(%)**	**Positive n(%)**	χ^2	**p-value**
Age			26.2129	0.000
Below 30	485(24.9)	49(43.4)		
30-39	854(43.8)	49(43.4)		
40-49	509(26.1)	14(12.4)		
50 and above	104(5.2)	1(0.8)		
ART status			3.8284	0.050
ART Naïve	157(8.0)	15(13.3)		
On ART	1795(92.0)	98(86.7)		
CD4 count			28.515	0.000
Below 200	294(15.1)	36(31.9)		
200-500	879(45.0)	53(46.9)		
500 and Above	779(39.9)	24(21.2)		

The patient characteristics of the patients assessed at the bivariate level were age, ART status, and CD4 count. Using Log-Rank Chi-square test, age and CD4 count were statistically significant to the cervical cancer screening among women living with HIV. Each of the three variables namely; Age, ART and CD4 count status checked in turn with the dependent variable cervical cancer screening result. All these were carried forward to the multivariate stage.

Determinants of Cervical cancer screening results

The determinants of ANC attendance were investigated using a binomial logistic regression on the characteristics of patients. Table 5.4 presents the likelihood estimates of cervical cancer screening outcome.

Table 5.4: Predictors of cervical cancer screening results

Independent variable		Odds Ratio	Confidence interval	p-value
Age				
	Below 30†	1.00	.	.
	30-39	0.55	0.12	<0.01
	40-49	0.28	0.89	<0.001
	50 and above	0.11	0.11	0.03
ART status				
	ART Naive†	1.00	.	.
	On ART	0.60	0.18	0.08
CD4 count				
	Below 200†	1.00	.	.
	200-500	0.51	0.12	<0.01
	500 and Above	0.26	0.07	<0.001
Constant		0.33	0.11	<0.001

† Represents reference category

The cervical cancer screening result outcome model was adjusted for age, ART status, and CD4 count. The predictors of cervical cancer screening result were age, ART status and CD4 count. ART status was not statistically related to cervical cancer screening outcome ($p>0.050$) however, age of the HIV positive woman screened and CD4 count were statistically significant to cervical cancer (($p < 0.05$).

Women who were aged between 30- 39 had reduced odds (OR= 0.55) of having a positive cervical cancer screening result when compared to their counterparts that are aged less than 30 years. Women who were aged between 40- 49 had reduced odds (OR= 0.29) of having a positive cervical cancer screening result when compared to their counterparts that are aged less than 30 years. Women who were aged between 50 and above had reduced odds (OR=

0.11) of having a positive cervical cancer screening result when compared to their counterparts that are aged less than 30 years.

Regarding CD4 count of patients, women who had CD4 counts between 200-500 had reduced odds (OR= 0.51) of having a positive cervical cancer screening result when compared to their counterparts that had less than 200 CD4 count. Also, women who had CD4 counts greater than 500 had reduced odds (OR= 0.26) of having a positive cervical cancer screening result when compared to their counterparts that had less than 200 CD4 count.

5.3 Cost Estimates of the Intervention

The table below shows the estimated institutional costs incurred by Mildmay-Uganda to screen one HIV positive woman. The cost screening of one woman was 2.45 USD and cost of cryotherapy was 16.833 USD.

Table 5.5: Costs of Screening

Category (A)	**Cost of items (Uganda shillings)**	**Dollar rate of each item (1USD=3600UGX)**	**Cost of screening one woman in UDS**
Clinical Utilization Items used			
Acetic acid	52,000 One litre bottle of which they use 5m per day. About 16-25 women are screened per day	8.9	0.058
Sponge holding forceps (sterilized after use)	4,000 used once	1.1	0.003
Distilled water	28,000 (20 liters of which one liter is used per day)	7.78	0.024
Cotton and gauze	12000 one roll per day	3.3	0.206
Gloves	10,000 a box	2.7	0.313
Kidney dishes (where acid and cotton swabs are placed)	55,500	15.41	0.04
Tissue	10,500 one per day	2.91	0.182
Bin for disposing off	19,000 apply depreciation	5.27	0.013

after use			
Bed linen	40,000 apply depreciation	11.11	0.037
Source of light e.g. overhead bulb	50,000 energy per month	13.66	0.034
Curtains	45,000 per pair apply depreciation	12.5	0.042
Forms for recording the findings	1500 one form per patient	0.1414	0.141
Chlorine solution for decontaminating	18,250	5.069	0.010
Labour for three nurses to conduct screening	900,000 each	0.5203	1.40
Sum			**2.45**

Table 5.6: Cost of cryotherapy as a form of treatment

Gas supply	490,000 of which the gas cylinder is used for one year	13.6	0.373
Speculum	22,000	6.1	6.10
Labour	900,000	250	0.260
Review care after cryotherapy	36,500		10.1
Sum			16.833

5.4 Cost-Effectiveness Analysis of the study

This was calculated as the differences in the total costs between the cost of screening all HIV positive women and the cost of screening HIV positive women who had voluntarily screened from 2012 to 2016, divided by the differences in life years gained between screening all women and life-years gained from HIV positive women who voluntarily screened. An incremental cost-effectiveness ratio (ICER) was calculated as from excel and its results are presented below;

Table 5.7: Deterministic results

Cost of screening all	**Cost of current strategy**	**Life years screen all**	**Life years under current strategy**	**Incremental cost**	**Incremental Benefit**	**ICER**
40337.6	5614.64	6024.1	5278.6	34722.9	745.6	46.6

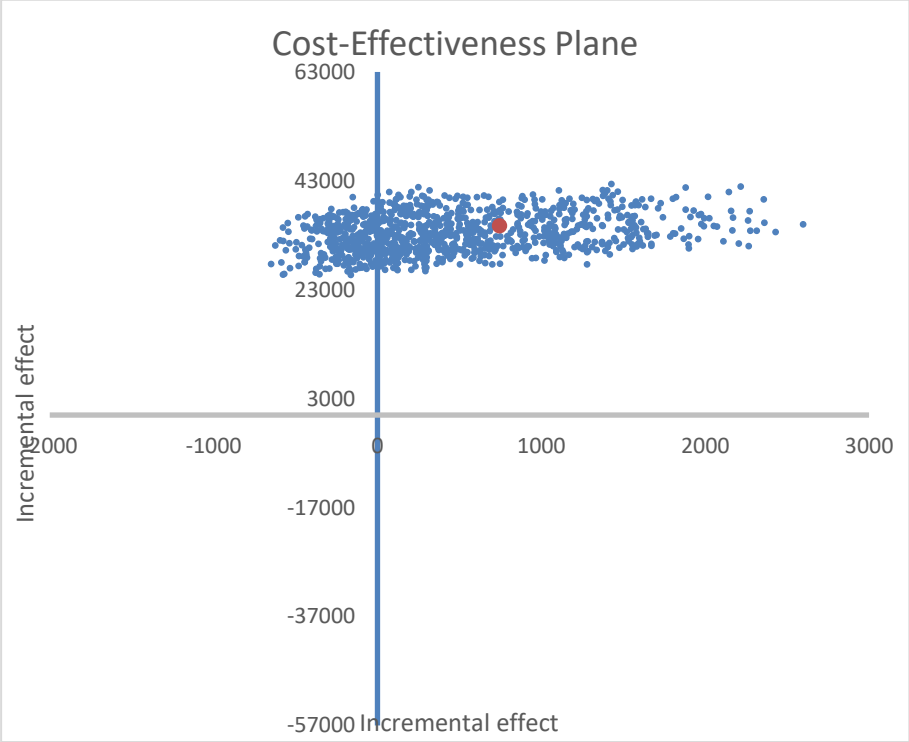
The ICER was 46.6 USD per a life-year gained from screening all women compared to the status quo. Finally, the Gross domestic product (GDP) per capita of Uganda for Uganda (2013) was used to determine the cost-effectiveness of integrating cervical cancer screening into HIV care. The program is determined to be cost-effective relative to *status quo* if the ICER is less than three times the GDP per capita. This criterion is consistent with the cost-effectiveness threshold used by the WHO (Nelson et al, 2016). The study determined that the cost effectiveness of integrating cervical cancer screening into HIV care was highly cost-effective.

The cost per positive screening result was estimated to 50 USD. This was obtained as result of the total cost screening under current strategy divided by the total number of positive cervical cancer results. The total cost under the new intervention indicates that the cost of screening is relatively low when all HIV positive women under go cervical cancer screening.

5.5 Probabilistic Sensitivity Analysis (PSA)

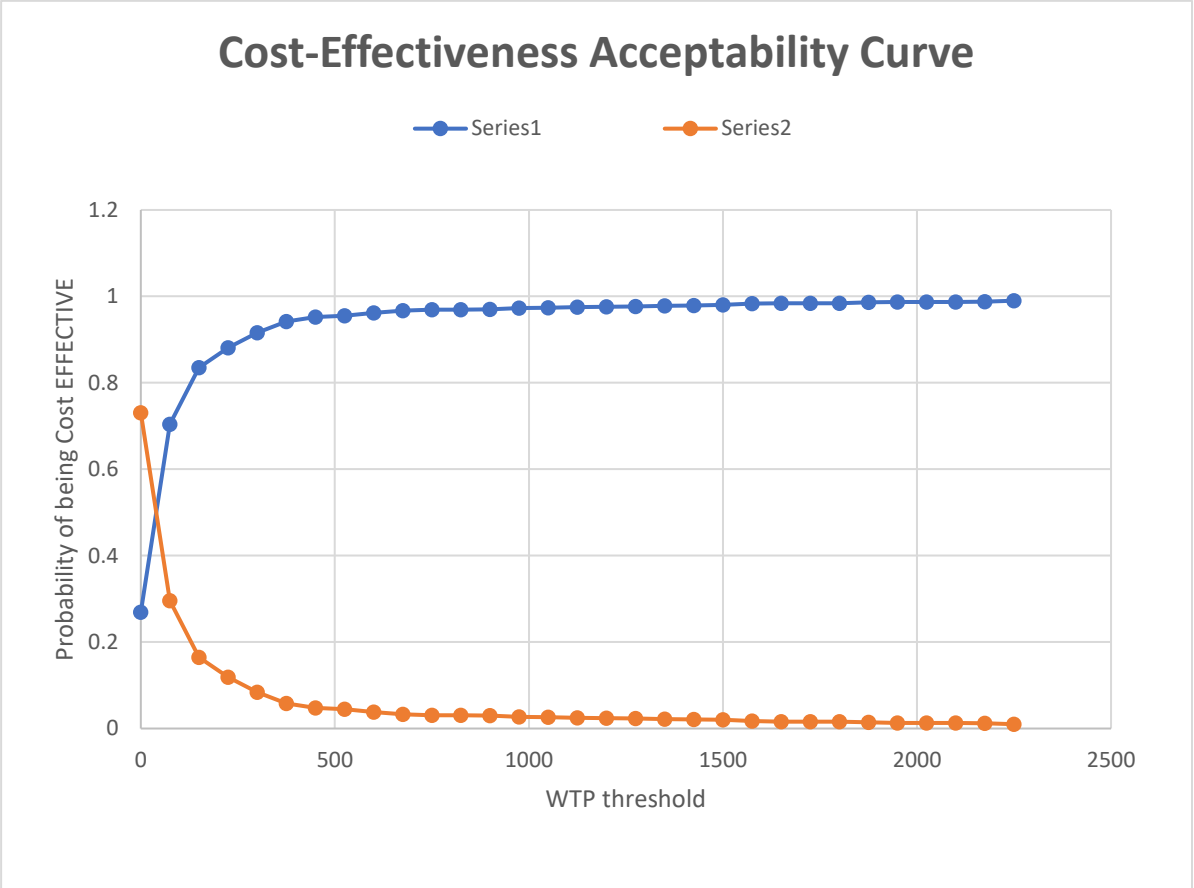
Results from the probabilistic sensitivity analysis were presented using a cost-effectiveness plane and CEAC. The cost-effectiveness plane shows differences in costs and effects between different interventions. Figure 1, shows the spread of pairs of incremental costs and incremental effectiveness values (ICERs) after running 1,000 Monte Carlo simulation.

Figure 2: Cost-Effectiveness Plane



From the above cost-effectiveness plane, almost 90% of the cost-effectiveness pairs are found in the northeast which suggests that the new intervention more effective and costly. However, a proportion (approximately 10%) of the points lie in the northwest indicating that new intervention is less costly and less effective than the *status quo*.

Figure 3: cost-effectiveness acceptability curve



The y-axis on the CEAC presented in Figure 2, indicates the probability that screening all HIV positive women (new intervention) is cost-effective compared to the status quo (voluntary screening), given the values of the Willingness To Pay (WTP) threshold on the x-axis. At the WTP threshold of zero USD per a life year, the probability that the new intervention being cost-effective was 0.0269. The probability of the old intervention being cost-effective was 0.731.

At 686 USD, the probability of the new intervention being cost-effective was 0.967. The WTP threshold increases when the probability of the new intervention being cost-effective increases beyond 750 USD thus the new intervention is cost-effective especially that the uncertainty surrounding the ICER is not much.

6 Discussion

This chapter discusses the research findings in relation to the research objectives outlined in Chapter Three.

The study indicated that the prevalence of HIV was highest among women aged 15-49 years and these accounted for 94.9% of the population. However, HIV women aged 30-39 years accounted for 43.7% of the total population and this was consistent to UNAIDS (2013). Similarly, the sample had an average age of 35.5 years. Mills (2011) noted that HIV women in Uganda aged 35 years on ART were likely to life more 22 years. This is comparable to the current life expectancy of 58.65 among HIV negative women. The study used 58.65 years to estimate the life-years gained from cervical cancer screening under current intervention. This is because outcomes of ART have tremendously improved among HIV patients during 5 years as discussed in the literature. Thus, the study assumed that HIV positive women have the same life expectancy as HIV negative women.

Similarly, HIV positive women are 2-12 likely to develop cervical cancer if CIN remains untreated. Bosch et al (2008) noted that untreated CIN II lesions have 50% chances to develop into cervical cancer within the first two years. This indicates the need for routine screening to detect and treat HSILs which may later develop into cervical cancer if not treated using cryotherapy. It also explains why the study assumed that HIV positive women with undetected CIN II had 0.83 chances of developing cervical cancer. This was based on the 5-year survival probability of cervical cancer in Tanzania. (Nelson et al, 2016). However, the primary study was not limited to only HIV patients.

These assumptions were incorporated into the analysis to estimate the life-years gained from screening. The resulted indicated that the integration of cervical cancer screening into HIV care in Uganda is highly cost-effective. It was likely to save the lives of many HIV women at a cost of 46.570 USD per a life-year gained. The lower costs of screening and treatment using cryotherapy in the study are comparable to other Sub-Saharan countries such as Kenya. Cryotherapy is one of the most affordable interventions of treating precancerous lesions. It is also suitable since it is done once the same visit.

The cost per positive screening result among women among HIV positive women was 50 USD was also cost-effective. The lower 5-year survival rates of 17.7% (Gondos et al, 2005), the extremely high costs of treating cervical cancer within a fragmented healthcare system and

the high prevalence of HIV in Uganda make screening and treatment of precancerous lesions using cryotherapy the most suitable intervention. Much as the treatment costs for treating the various stages of cervical cancer have not yet been estimated in Uganda, these can be assumed to almost like those of the Ocean Road Cancer Institute (ORCI) in Dar-es-Salaam, Tanzania. These are estimated to be 2526.06 USD (Nelson et al, 2016) such costs are extremely high for most low-income families as well as the state whose healthcare budget is less than 10% of the total GDP. Furthermore, high rates cervical cancer undermines the achievements of ART by lowering the life expectancy of HIV positive women.

Cervical cancer screening is an affordable process that reduces the agony that comes with treating cervical cancer whose survival probability is low. Women play an important role in nation building and the early loss of women due to cervical cancer renders many children orphans, deprives families of future incomes and increases poverty since families with cervical cancer patients must spend a lot of their incomes and savings to access treatment. These factors explain why the intervention should be adopted and implemented across various HIV care centres.

6.1 Challenges Facing Effective integration of cervical cancer screening in Uganda

Basing on the responses from the questionnaire that was answered by the nurse in charge of cervical cancer screening at Mildmay Uganda, the following challenges were identified to have hindered the integration of cervical cancer screening into HIV care at Mildmay-Uganda.

1) Basing on the literature, it is eminently clear that the uptake of cervical cancer screening is very low among women regardless of their HIV status. Some of the factors that have hindered effective integration of cervical cancer arise from the poor health system as explained in chapter three of the study. According to the key respondent, it was found out that Mildmay Uganda has 16 centres in various districts but cervical cancer screening is only done at the main centre which is in Lweza-Wakiso district. More so, the utilization of the screening services at main centre remains very low. Less than 25% of the entire HIV positive women accessed cervical cancer screening at Mildmay-Uganda from 2012 to 2016. The low screening patterns have been reported by Ndejjo et al (2016), Kamulegeya, Bukenya & Makumbi (2014) among others. The main obstacle that has hindered the effective integration of cervical

cancer into HIV care within that various centres is the lack of sufficient resources to purchase the equipment to conduct cervical cancer screening. However, the current staff within these centres has been trained on how to conduct cervical cancer screening. The issue of inadequate resources to purchase screening equipment does not only affect Mildmay Uganda but it is a national problem which emanates from the chronic underfunding of the healthcare sector. Various health centre IV and regional referral hospitals do not provide cervical screening due to lack of resources.

2) One of the important aims of HIV care or treatment is to prolong life for those under care. This requires initiating various mechanism reduce the risk of chronic or infectious diseases among those under HIV care. It involves effective care management among diagnosed with certain diseases such as Tuberculosis, cervical cancer among others. Therefore, effective integration cervical cancer screening does not start with and end with screening but it needs an effective follow-up for those patients who are been confirmed or suspicious for cervical cancer to ensure that they have received treatment at the referral hospitals. This is because the high stigma among HIV positive women is likely to deter them from accessing further cervical cancer treatment at various referral hospitals even after screening. Unfortunately, all HIV care centres that provide cervical cancer have no mechanism for follow up for those patients who are sent to referral hospital as wells as ensuring that those who have been screened come back on their next appointment after one year.

6.2 The relationship between cervical cancer and age, treatment and CD4

The description of the patient characteristics in table 5.2 indicated that the prevalence of HIV/AIDS is highest among women ≥15 years. These accounted for 94.9% of the total number of HIV/AIDS infections that were registered in the study. Specifically, the results indicated that women aged 30 to 39 years had the highest percentage of HIV/AIDS (43.7%). This is further supported by studies such as the UNAIDS (2014) that most HIV infections occur among women aged between 15 and 49 years in Uganda.

Furthermore, majority of the patients were on ART (91.7%). This is partly in line with HIV/AIDS treatment guidelines that were introduced in 2015 by WHO, which states that all people testing positive for HIV must be enrolled on ART regardless of their CD4 count. This is a positive strategy towards ensuring that those with HIV/AIDS can live

longer and healthier life. Similarly, 94.5% (1952) had negative cancer result and 5.5% (113) had positive cervical cancer lesions. This indicated a low prevalence of cervical cancer among HIV/AIDS women among those who screened.

The biggest proportional (45.1%) of the 2,065 patients had a CD4 count between 200-500, (38.9%) had a CD4 count of 500 and above and only 16% (330) had a CD4 count below 200. Only 16.1% of the patients had a higher risk of having HIV progressing to AIDS. It is worth noting that 84% of the patients had a CD4 which was over 200 which considerably shows that patients were in good health partly. Age and CD4 count was statistically significant to cervical cancer screening among women positive women. This is supported by a number studies such as Palefsky, et al (1999), Jaquet et al (2012) who noted that HIV-positive women with a CD4 count <200 cells mm3 or between 200 and 499 cells mm3 were more likely to harbour an oncogenic HPV compared with women with a CD4 count ⩾500 cells mm3.

6.3 Limitations of the study

The study had several limitations which influenced the life-years gained and the ICER, these mainly originated from the assumptions made. These included;

The estimation of life-years gain using from screening using survival probabilities from Tanzanian study limited the study. Furthermore, Tanzanian study (Nelson, et al, 2016) adopted these estimates from a South African study. It is important to note that the progress from screening and treatment relating to cervical cancer amongst these countries is relatively different. Thus, this explains why these countries have various incidence, mortality and survival rates. According to Africa Health, Human & Social Development Information Service (2014) Tanzania and Uganda have higher incidence of cervical cancer by age standardized rate than South Africa. On the contrary, South Africa is likely to have higher survival rates of cervical cancer due to its better health care system than Tanzania and Uganda. Therefore, assumption that Uganda has similar survival probabilities for stage one of cervical cancer like South Africa limited the study.

The scope of the data collected limited the study. Data was only collected from Mildmay-Uganda. It also limited understanding various key aspects relating to the study such the prevalence of CIN II among HIV women. However, the decision to collect data only from

Mildmay- Uganda was done because the researcher could not finance collecting data from other HIV/AIDS centres in Uganda.

The estimation of cost-effectiveness from the provider perspective also limited the study. Much as screening of cervical cancer is free and the cost-effectiveness of integrating it in HIV care from the provider perspective has been determined to cost-effective, the societal perspective needs to be determined since various factors or costs from the society point of view influence the decision HIV women to seek cervical screening.

6.4 Related studies and further research

Much as the several studies do indicate that HIV positive women 2-12 times more likely to get cervical cancer due to the similarities in risk factors between the two diseases, few studies have been done to establish the cost-effectiveness of integrating cervical cancer screening into HIV-care within developing countries. Kamakech et al (2015) asserted the integration of cervical cancer into HIV care was a feasible approach. Huchko (2012) noted that the integration of cervical cancer into HIV care was cost-effective and screening with a single-lifetime "see and treat" visit with VIA and cryotherapy most cost-effective compared to no treatment leading to 32.30 USD per QALY. As far as, I know this is the first study that seeks to establish the cost-effectiveness of integrating cervical cancer screening into HIV care in Uganda. The model framework in this study provides evidence to policy makers to allocate more resources to ensure that various HIV care centres can provide cervical cancer screening. It also provides a basis for further studies such as the 5-year survival probability of cervical cancer among HIV women, attitude, level of awareness of cervical cancer screening among HIV positive women and their perceptions towards cervical cancer screening and the treatment follow up of HIV patients diagnosed with cervical cancer.

6.5 Ethical considerations

A research proposal was sent to the Institutional Review Board (IRB) of Mildmay-Uganda and it requested me to make a few changes in the proposal. Thereafter, the research proposal was accepted and the IRB committee granted me an approval letter that was later forwarded to the Uganda National Council of Science and Technology upon which I was granted a research permit.

6.6 Recommendations

For any screening program for be effective, it should cover at 75% of the targeted population. Massive sensitization is an imperative aspect towards achieving this target. Scholars like Kamulengeya et al (2014) noted that several women regardless of their HIV status lack knowledge relating to the advantages of early cervical cancer screening. Various HIV/AIDS organization and donors need to integrate the messages or campaigns of cervical cancer screening within their HIV/AIDS programmes. These messages should not only target women but also their partners so that they understand the advantages of early or routine cervical cancer screening. For example, mobile HIV screening campaigns should be integrated with cervical cancer screening. This will reduce the various public misconception relating cervical cancer screening where many people assume that cervical cancer is untreatable.

Most patients who receive cervical cancer screening within HIV care centres are permanent clients to these hospitals since they routinely come for HIV care. Therefore, a follow up mechanism for those patients who are sent to referral hospitals needs to be established. This can be done through the following ways; the cervical cancer results from referral hospitals should be written on the patient files during their subsequent visits. This will help Mildmay-Uganda and other HIV care centres to know intensity of cervical cancer of these respective patients. It will also indirectly work has a confirmatory notification that these patients have begun receiving referral treatment.

The integration of cervical cancer screening into HIV care cannot take place in a vacuum but within well-established HIV care centres. Thus, the improvement in the screening patterns and the sustainability of its benefits among HIV positive women hinges on the provision of effective HIV care. This includes timely access of ART and reduction of stigma. Huge discrepancies in the availability of HIV care and treatment continues to exist. By 2015, at least 40% of adults living with HIV were still not on treatment. Poorly established healthcare centres dominate the rural setting and such centres can hardly provide cervical cancer screening even if the two were to be integrated. The upgrading or improvement of the entire infrastructure of healthcare centres is indispensable aspect towards integrating cervical cancer screening into HIV care. For effective integration of cervical cancer screening to take off these gaps need to be filled.

6.7 Conclusion

Based on the evidence from the study, the integration of cervical cancer into HIV care using VIA and treatment of pre-cancer lesions using cryotherapy is highly cost effective. It provides an opportunity to HIV positive women to receive cervical screening and treatment of precancerous lesions using cryotherapy which would have developed into cervical cancer if left untreated. This reduces the economic burden of cervical cancer especially that its treatment is extremely expensive. However, its implementation and effectiveness depends on the setting up a framework which will reduce the barriers surrounding cervical cancer screening in Uganda.

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