Prevalence of and risk factors for cervical precancerous lesions in HIV positive 20–49-year-old women attending ART clinic in the Zambezi region of Namibia

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A mini-thesis submitted in partial fulfillment of the requirements for the degree of Master in Public Health at the school of Public Health. University of the Western Cape

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November 2022

DECLARATION

This work has not been previously submitted in whole, or partly for any degree. It is my own work. Any sources that I have used or quoted have been cited and referenced.

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ACKNOWLEDGEMENTS

This page is dedicated to Prof. Zandile June-Rose Mchiza, the Zambezi Regional Health Directorate team, the study participants, Nyarai Mpariwa and Kristian Mpariwa

ABSTRACT

Background: By 2020 cervical cancer was the fourth most prevalent cancer in women worldwide. In Africa, cervical cancer is the second most prevalent malignancy with the highest incidence in Sub Saharan Africa (SSA). Cervical cancer was reported to be the second most prevalent cancer in Namibia from 2010 to 2014. On the other hand, SSA has the highest global burden of human immune deficiency virus (HIV) which predisposes individuals to persistent human papilloma virus (HPV) infections. Human papilloma virus infections promote the development of precancerous lesions that may later lead to cervical cancer. **Aim:** The aim of the proposed study therefore was to determine the prevalence and risk factors for the development of cervical precancerous lesions in women living with HIV (WLHIV) who accessed health services at Katima Mulilo Hospital antiretroviral therapy (ART) clinic in the Zambezi region of Namibia. The precancerous lesions were diagnosed through visualisation of the cervix under acetic acid (VIA). **Methodology:** This was a cross-sectional study of 300 eligible WLHIV aged 20 to 49 years. They were randomly selected from the afore mentioned clinic's cervical cancer register. Clinical, sociodemographic, behavioral and reproductive risk related data was collected from the patient care booklets, electronic patient monitoring systems, cervical cancer screening registers and interviewer administered standardized questionnaire. The data was collected on an Excel spreadsheet and analysed using IBM SPSS statistical package (version 28). A Chi-square analysis was used to determine if there were significant differences in VIA outcomes among the screened WLHIV. Binary logistic regression analysis was then conducted to determine the level of association between the clinical, sociodemographic, behavioral and reproductive risk related data and the VIA outcomes. The associations were then assessed using the adjusted odds ratio, confidence intervals which did not overlap and p values <0.05 were considered significant. **Results:** Overall, the prevalence of cervical precancerous lesions among the participants was 19.7%. Having four or more

lifetime sexual partners increased the likelihood of developing cervical precancerous lesions by almost three folds when compared to being in monogamous relationships (AOR= 2.797, 95% CI: [1.302-6.009], p=0.008.). Delaying sexual debut to older than 16 years reduced the likelihood of developing cervical precancerous lesions by 78.8% (AOR=0.212, 95% CI: [0.082-0.547], p=0.001 when compared to engaging in sexual debut at 16 years or less. Delaying marriage to ages older than 18 years reduced VIA positivity by 69% (AOR=0.310, 95% CI: [0.114-0.841], p=0.021). Women who were on ART for more than five years were also less likely to be VIA positive (AOR=0.366, 95% CI: [0.177-0.755], p= 0.007) compared to those who were on anti-retroviral therapy (ART) for less than five years. **Conclusions:** While HPV-DNA screening and HPV vaccination among adolescent girls were beyond the scope of the current research, due to the high prevalence rates of cervical precancerous lesions observed in current research, there is need to consider introducing these surveillance and intervention strategies, especially among WLHIV. In fact, interventions directed at delaying sexual debut, marriage and promoting stable on ART uptake, showed promise to reduce the likelihood of developing cervical precancerous lesion among WLHIV. Hence, the afore-mentioned risk factor outcomes highlight the need to endorse and strengthen programs to counter structural challenges which predispose women to HIV, early sexual debut and early marriage including multiple sexual partners.

KEY WORDS

Cervical cancer

Precancerous lesions

Visualisation of the cervix through acetic acid (VIA)

Women living with HIV (WLHIV)

Screening

Prevalence

Risk factors

Sub Saharan Africa

Namibia

Human Papilloma Virus (HPV)

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ABBREVATIONS

Table 1. Abbreviations used in this study

AGYW	Adolescent girls and young women
ART	Antiretroviral therapy
COC	Combined oral contraceptive
DHS	Demographic health survey
FSW	Female sex worker
HIC	High income countries
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
ICC	Invasive cervical cancer
IUCD	Intrauterine contraceptive device
LHDI	Lower human development index
LIC	Low-income countries
LMIC	Low- and middle-income countries
MI	Middle income country
MoHSS	Ministry of Health and Social Services
NCD	Non communicable diseases
Pap smear	Papanicolaou smear
POP	Progesterone only pill
SDI	Sociodemographic index
SSA	Sub Saharan Africa
WHO	World Health Organization
WLHIV	Women living with HIV

DEFINITIONS FOR THIS STUDY

Cervical cancer: This is when the cells on the surface of the cervix multiply bypassing the body's auto regulation thereby overwhelming normal cells and function. If untreated they spread to the surrounding tissue, beyond the pelvis and eventually lead to death.

Precancerous lesions: These are abnormal epithelial cells covering the cervix which if they continue to grow unchecked will lead to invasive cervical cancer.

VIA: A cervical cancer screening method alternative to the Pap smear method used in resource constrained settings where the cervix is soaked with acetic acid for one minute. A positive result will show a whitish lesion on the cervix if observed using a bright light. An advantage of this procedure is that a precancerous lesion can be treated in one sitting

Cervix: This is the lower third of the uterus, in a non-pregnant woman of child bearing age it measures approximately 3cm in length and 2.5cm in diameter, the lower part lies within the vagina and is visible with a speculum

HPV: This is an easily transmissible DNA virus, there are more than 150 of them, different types cause different infections in different parts of the body. Some may cause genital or skin warts. Most of the time the infection clears (91%). If the infection persists, it may lead to the development of cancer

High risk HPV: These are types of human papilloma virus which have the ability to cause the cells in the infected host to change and become pre-cancer cells. The majority of cervical cancers are caused by high-risk HPV infection

CHAPTER 1: INTRODUCTION

1.1 Background

Cancer research is gaining prominence worldwide partly due to increasing mortality rates associated with non-communicable diseases (NCDs) worldwide which now account for 74% of all deaths (WHO, 2022). According to the global cancer statistics of 2020; cervical cancer is the fourth most prevalent malignancy and the fourth most prevalent cause of death worldwide (Sung *et al.*, 2021). In 2018 it was estimated that there were 570 000 new cancer cases and 311 000 deaths due to cancer worldwide, ninety percent of these new cases and 85% of deaths were estimated to be from Sub Saharan Africa (SSA) (Zhang *et al.*, 2021). While trends in cervical cancer incidence and mortality between 1990 to 2019 have decreased for most sociodemographic index (SDI) areas particularly in Central and Latin America, cervical cancer attributable morbidity and mortality increased in SSA countries like Lesotho and Zimbabwe (Zhang *et al.*, 2021). Moreover, in low- and middle-income countries (LMICs); women who suffer from cervical cancer are twice more likely (60%) to die from cervical cancer than their counterparts in high income countries (HICs) (WHO, 2020). The declining trends in morbidity and mortality due to cervical cancer in HICs are attributed to improved access to health care, higher education levels, changes in marriage age and family planning behaviour (Zhang *et al.*, 2021). To highlight the issues raised by Zang *et al.* (2021); Kuguyo *et al.* (2017) in their publication stated that in Zimbabwe like many SSA countries the high burden of cancer can be attributed to access to health services, poor screening and diagnosis, inadequate treatment options and high human immune deficiency virus (HIV) prevalence rates. In Namibia the age adjusted incidence rate for cervical cancer for 2021 was 28.6 per 100 000; compared to (36 and 13) per 100 000 for Southern Africa and around the globe, respectively. According to Bruni *et*

al. (2021), women in Namibia were almost two times more likely than the rest of the world to be diagnosed with cervical cancer.

Moreover, Ali-Risasi *et al.* (2015) have long suggested that, for malignant transformation to occur in the cervical epithelium, persistent infection with high-risk HPV has to occur. The high-risk infections caused by HPV types 16 and 18 are associated with 70% of all cervical precancerous lesions and cancers (Ali-Risasi *et al.*, 2015). According to the World Health Organization (WHO, 2020), the most widespread STI is HPV. Worldwide the pathogenesis of both precancerous lesions and invasive cervical cancer (ICC) is identical (WHO, 2020). The difference in burden is due to lack of quality screening and treatment facilities and services in LICs (WHO, 2020). If primary and secondary prevention methods like HPV vaccination and screening are adopted, this disease is nearly completely preventable (Sung *et al.*, 2021). France, Norway, Ireland and other HICs adopted programs to administer broad spectrum HPV vaccines to adolescents and screening for adults (Kuguyo *et al.*, 2017). Kuguyo *et al.* (2017) goes on to affirm that this has led to reductions in cervical cancer incidences unlike in SSA where these interventions are not adequately implemented.

According to MoHSS (2018), human papilloma virus infections can persist for up to twenty years before the development of ICC. During this time HPV may induce the formation of abnormal lesions on the cervix, these precancerous lesions can be detected through screening and this will offer an opportunity to prevent ICC (MoHSS, (2018). The screening tests currently recommended by the World health organization are the (WHO) are Papanicolaou (Pap) smear, visualisation of the cervix under acetic acid (VIA) and HPV-deoxyribonucleic acid (DNA) testing (WHO, 2021). Pap smear screening has been instrumental in reducing ICC incidence in

HICs; however, the implementation has not been very successful in LMICs partly due to shortages in qualified human resource personnel and infrastructure to process the samples (Kuguyo *et al.*, 2017; Sung *et al.*, 2021). In 2018 the Namibian Ministry of Health and Social Services (MoHSS) launched a program to screen women living with HIV (WLHIV) aged 20 to 49 using the VIA method (MoHSS, 2018). Globally, of the 33 000 new cases of ICC diagnosed in 2018, 20 000 were attributable to HIV infection (Stelzle *et al.*, 2021). The time from HPV infection to the development of ICC is shorter in WLHIV compared to their HIV negative counterparts (MoHSS, 2018). Women living with HIV are several times more likely to have persistent HPV infection as well as being up to six times more likely to develop ICC which is also more likely to develop at a younger age (WHO, 2020). The above risks relating the development of ICC with HIV infection were the reason that the Namibian MoHSS decided to prioritize the screening of WLHIV.

The VIA screening method involves visualisation of the cervix using a naked eye after applying 5% acetic acid; this is a simple procedure which can be performed by trained medical staff and can be followed with immediate treatment while using minimal equipment (MoHSS, 2018). A VIA positive result indicates the presence of a cervical precancerous lesions, which will stain white on exposure to acetic acid, in a VIA negative result the cervix retains a normal pink colour (Gabaza *et al.*, 2019). Compared to Pap smear testing, VIA is cheaper and therefore much preferred by programs for use in LMIC for mass screening (Gabaza *et al.*, 2019). The WHO global strategy for cervical cancer elimination recommends the HPV-DNA based test; because it is able to detect high risk HPV strains which cause ICC (WHO, 2020). Unlike tests which rely on visual inspection and clinician judgement, the HPV-DNA test is regarded to be a more objective, simpler and efficient procedure that supports the preventing cervical cancer more than VIA or Pap Smear (WHO, 2021). However, HPV-DNA testing is not yet operational

in Namibia and the currently recommended test by the MoHSS is the VIA test for mass screening (MoHSS, 2018).

1.2 Problem statement

Ali-Risasi *et al.* (2015) has long admitted that data on prevalence and mortality due to cervical cancer is either missing or sparse in most but not all SSA countries. Kuguyo *et al.* (2017) further suggested that a significant number of cervical cancer cases may occur unreported due to the fact that some of the most affected have very little access to healthcare facilities. There are several publications describing the prevalence of cervical precancerous lesions in WLHIV in several SSA countries (Ali-Risasi *et al.*, 2015; Izudi, Adrawa and Amongin, 2016; Belayneh, Mitiku and Weldegebreal, 2019). To our knowledge there is only one publication describing the prevalence of cervical precancerous lesions in WLHIV in Namibia and is referred to below. This publication used pooled data from 8150 women who were screened for cervical cancer using the VIA method from 2018 to 2020 (Korn *et al.*, 2022). The outcomes were that the via positivity in WLHIV was 17% compared to 15% positivity in their HIV negative counterparts, the difference was significant p=0.02 using the Chi-square test (Korn *et al.*, 2022). However, this publication did not present the risk factors for the development of cervical pre-cancerous lesions in WLHIV (Korn *et al.*, 2022); despite Namibia having a generalized HIV epidemic with an overall prevalence of 12.6% among the 115 to 64 age group, where 15.7% is among females and 9.3% is among males) (MoHSS, 2019). The prevalence of precancerous lesions in WLHIV across SSA differs between countries for example 22,9% in Eswatini, 13.7% in Zimbabwe, and 20.2% in Ethiopia (Jolly *et al.*, 2017; Gabaza *et al.*, 2019; Kassa *et al.*, 2019). While Korn *et al.* (2022) describes the prevalence of precancerous lesions of the cervix in WLHIV in Namibia, to our knowledge no publication has described the relationship between risk factors and the development of precancerous lesions of the cervix in Namibia. Hence, the

current study aimed at adding to the body of knowledge on the prevalence and the risk factors for precancerous lesions of the cervix in WLHIV at Katima Mulilo ART clinic. The risk factors were classified into clinical, sociodemographic, behavioral and reproductive risk factors. The study is hoped to bridge the afore mentioned research gaps.

1.3 Aim

This study aimed to determine the prevalence and risk factors for the development of precancerous lesions of the cervix among WLHIV aged 20 to 49 years also receiving health care at Katima Mulilo ART clinic in Namibia.

1.4 Objectives

- To determine the **reproductive risk factors** associated with the development of precancerous lesions of the cervix in WLHIV aged 20 to 49 attending Katima Mulilo ART clinic.
- To determine the **clinical risk factors** associated with the development of precancerous lesions of the cervix in WLHIV aged 20-49 attending Katima Mulilo ART clinic.
- To determine the **sociodemographic risk factors** associated with the development of precancerous lesions of the cervix in WLHIV aged 20 to 49 years attending Katima Mulilo ART clinic.
- To determine the **behavioral risk factors** associated with the development of precancerous lesions of the cervix in WLHIV aged 20 to 49 years attending Katima Mulilo ART clinic.

1.5 Study Purpose

The study purpose was to contribute to the knowledge and understanding of the prevalence of and risk factors for the development of cervical precancerous lesions in WLHIV between the ages of 20 to 49 years at Katima Mulilo ART clinic. Understanding the prevalence of precancerous lesions will guide program managers at national level to appropriately allocate resources according to the burden of disease to adequately screen, manage and prevent the development of ICC. Knowing the types of risk factors to the development of precancerous lesions in WLHIV will add insight into possible recommendations to the National HIV Treatment Guidelines and Cervical Cancer Screening Guidelines concerning the prevention, screening and treatment of cervical pre-cancerous lesions. Risk factor data obtained in this study will assist in describing the different vulnerable populations and their characteristics. It will also help policy makers to conduct further research on the structural factors which predispose WLHIV to develop precancerous cervical lesions. Prevalence studies like this one shed light into the burden of disease and distribution; this is often used to inform policies proven to prevent cervical cancer, among them being HPV vaccination roll out and HPV-DNA based screening and mapping out in priority areas (Sedgwick, 2014; Korn *et al.*, 2022). Understanding the trends, prevalence and risk factors associated with the development of cervical pre-cancerous lesions may also stimulate further similar research in SSA. Such research may be undertaken by health care workers, partners or program managers in these countries and regions.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

The literature review below outlines the global burden of cervical cancer and the difference in burden between HIC and LMIC while linking that to the levels of response in terms of the prevention, screening and treatment of precancerous lesions of the cervix in women. The review will also look at the evidence on the prevalence and risk factors for cervical precancerous lesions among women in Africa and SSA. Among these factors are the sociodemographic, reproductive, behavioural and clinical determinants of health. Initially, the literature review will look at how the prevalence of precancerous lesions differ across African countries, regions and population groups. The review will then attempt to illustrate the gaps in response to screening and treatment in some regions or countries in Africa and how they contribute to the high burden of ICC in these areas. The literature will also be used to explore some of the recognized common risk factors and how they affect the prevalence of abnormal lesions of the cervix with emphasis on WLHIV.

2.2 Search strategy

Keywords and phrases identified and used were *Prevalence, risk factors, HIV positive women, Human Papilloma Virus, cervical precancerous lesions, Africa, sub-Saharan Africa, southern Africa, cervical cancer screening, screening, VIA, acetic acid, Namibia*. The search platforms used were PubMed, PLOS and BioMed Central. The Boolean operators used were AND and OR according to the information nature of the desired outcome. One filter was used, which was for free articles.

Table 2. Literature captured and used in the literature review

Author	Type of document	Geographic area
Ali-Risasi *et al.* (2015)	cross sectional	DRC
Belayneh, Mitiku and Weldegebreal (2019)	cross sectional	Ethiopia
Bray *et al.* (2018)	report	Global cancer report
Brisson *et al.* (2020)	mathematical modelling	LI and LMICs
Bruni *et al*. (2021)	report	Namibia
Chichareon *et al*. (1998)	case control	Thailand
Chin'ombe *et al.* (2014)	report	Zimbabwe
Durowade *et al.* (2012)	cross sectional	Nigeria
Taye, Mihret and Muche (2021)	case control	Ethiopia
Roura *et al.* (2016)	cohort	Multi center-Europe
Jolly *et al.* (2017)	cross sectional	Eswatini
Kassa *et al.* (2019)	cross sectional	Ethiopia
Korn *et al.* (2022)	cross sectional	Namibia
Lemu *et al.* (2021)	cross sectional	Ethiopia
Liu (2018)	systematic review and meta-analysis	Europe, Africa, United States
Loue *et al.* (2009)	systematic review and meta-analysis	Africa, Asia, South America
Macleod and Reynolds (2021)	scoping review	Eastern and Southern Africa
Moreno *et al*. (2002)	systematic review	South America, Asia, Africa, Europe
Namale *et al*. (2021)	cross sectional	Uganda
Nkfusai *et al.* (2019)	cross sectional	Cameroon
Ono *et al.* (2019)	correspondence	N/A
Ramogola-Masire *et al.* (2022)	cross sectional	Botswana
Suehiro *et al.* (2021	cross sectional	Brazil
Singini *et al.* (2021)	case-control	South Africa

Stelzle *et al*. (2020)	systematic review	Africa, Asia, Europe, North America
Tsehay and Afework (2020)	Systematic review and meta-analysis	Ethiopia
Weldegebreal and Worku (2019)	systematic review and meta-analysis	sub–Saharan Africa
WHO, (2020)	policy document	
WHO, (2021)	Treatment guideline for national programs	

2.3 Global overview regarding precancerous lesions and cervical cancer

Invasive cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of death in women worldwide, with over 600 000 new cases and causing almost 350 000 deaths worldwide in 2018 (Sung *et al.,* 2021). The incidence and mortality due to ICC have been declining in most parts of the world due to increasing socioeconomic levels associated with improved hygiene, lower parity and declining incidence of sexually transmitted infections (Sung *et al.,* 2021). Disparities in screening for and treatment of precancerous lesions of the cervix contribute to the high burden of ICC in developing countries (Tsehay and Afework, 2020). Tsehay and Afework (2020) to support the above assertion go on to state that almost 80% of women in Europe and the United Sates are screened for cervical cancer every 5 years while only 5% of women in LMIC are screened for precancerous lesions of the cervix.

2.4 Burden of disease regarding precancerous lesions and cervical cancer in Africa

In lower human development index (LHDI) countries ICC ranks second in incidence and mortality second only to female breast cancer (Bray *et al.,* 2018). The above observations are

partially true for Namibia, as ICC is the second leading cause of death in women while breast cancer is the leading cancer to be diagnosed as of 2018 (Bruni *et al*., 2019). One of the areas with the highest morbidity due to cervical cancer is SSA, this is due to limited health knowledge about the disease and the lack of screening and treatment facilities (Zhang *et al*., 2021). Zhang *et al.* (2021) hypothesizes that culture and conservative sexual practices on the other hand may be contributing to the low prevalence of ICC in North Africa and the Middle East. While there have been reductions in the prevalence of ICC cases in the Maldives, Taiwan and Singapore due to effective screening programs, there have been increases in mortality in SSA countries like Kenya, Malawi, South Africa and Zimbabwe (Bray *et al.*, 2018*;* Sung *et al*.,2021).

HPV is an important determinant in the development of ICC as shown in an early case control study which demonstrated that the fraction of risk attributable to HPV infection in squamous cell and adenocarcinomas ICC was 95% and 89% respectively (Chichareon *et al*., 1998). The above observation was also replicated in a population of WLHIV in SSA where in Harare 98% of cervical swabs taken from WLHIV who had ICC were positive for HPV genetic material (Chin'ombe *et al.*, 2014). There were almost 18 million WLHIV in 2018; 60% of them lived in eastern and southern Africa, these women were are up to six times greater risk of developing ICC than their HIV negative counterparts, making it the most frequently detected cancer in WLHIV (Stelzle *et al.*, 2021). There is a high HPV and ICC prevalence in WLHIV, it seems HPV acquisition is increased with HIV infection, HIV reduces epithelial clearance of HPV while promoting its persistence in the cervical epithelium (Liu *et al.*, 2018). In a case-control study conducted in Johannesburg, 3450 women with ICC were compared with 5907 controls, being HIV positive had a population attributable fraction of 17.6%, higher than educational attainment and parity (16.2% and 12.6%) respectively (Singini *et al.*, 2021).

In a systematic review and meta-analysis, the pooled prevalence of precancerous lesions in WLHIV in SSA from cross-sectional study data in different hospital settings from different countries was 25.6%, 95% CI: (19.4%-31.8%) in 2019 (Weldegebreal and Worku, 2019). Prevalence data for cervical precancerous lesions in SSA is very variable, this is thought to be due to differences in sexual practices and varying availability of quality screening and treatment options available (Nkfusai *et al.*, 2019). The above variability is also observable when comparing the prevalence of lesions in WLHIV versus their HIV negative counterparts as shown below. In Eswatini cervical lesions were present in 22.9% of WLHIV compared to 5.7% in HIV-negative women, while in the Democratic Republic of the Congo the findings were at 31.3% prevalence versus 3.9% in WLHIV and HIV-negative women, respectively (Jolly *et al*., 2017; Ali-Risasi *et al*., 2015). The results from Namibia further highlight this variability in the prevalence of cervical lesions; WLHIV had a prevalence of 17% compared to 15% in their counterparts who were HIV-negative (Korn *et al*., 2022). The extreme variability in the prevalence data pulled from Africa shown above warrants for more national studies in Africa that would support the distribution of resources for optimal cervical cancer control and eventual elimination of this disease from the continent.

2.5 Factors associated with the development of cervical precancerous lesions and cervical cancer in Africa

It has been established that precancerous lesions of the cervix have a high potential to progress to ICC, and HIV increases the likelihood of this occurring including shortening the time to the development of malignancy (MoHSS, 2018). Therefore, it is also important to determine the nature of associations of ICC, precancerous lesions and HIV within different populations with

different characteristics. This would therefore support targeted approaches for cancer screening amidst scarce resources and promote sexual and behaviour change in most LMIC and Africa. There is an abundance of evidence suggesting that cervical precancerous lesions are more prevalent in WLHIV when compared to their HIV-negative counterparts as shown below. In different countries positivity for precancerous lesions was higher in WLHIV when compared with HIV negative ones; In Zambia it was 40% versus 20%, in South Africa it was 14% versus 5% while in Tanzania it was 8% versus 2% (Korn *et al.*, 2022). The sections below therefore will outline the literature that explains the relationship between cervical precancerous lesions and reproductive, behavioral, clinical and sociodemographic risk factors.

2.6 Reproductive risk factors

2.6.1 Parity

Increasing parity has been shown to increase the odds of developing precancerous lesions of the cervix, there are several publications which have been able to demonstrate this relationship and also some theories to the pathogenesis as described below. In a cross-sectional study in Ethiopia, it was found that having more than two pregnancies increased the odds of developing precancerous lesions of the cervix, this was also consistent with results from previous studies done in Tanzania and Côte d'Ivoire (Belayneh, Mitiku and Weldegebreal, 2019). Belayneh, Mitiku and Weldegebreal (2019) also postulated that repeated lacerations on the genital wall provided entry points for HPV infection which promotes precancerous lesion formation. In a systematic review by Weldegebreal and Worku (2019) it is shown that the likelihood for the development of precancerous lesions of the cervix in WLHIV increases by almost 2 folds (OR: 1.8) if they have more than two child births. In pregnancy, hormone induced changes in the cervical epithelium may promote exposure to HPV while pregnancy induced

immunosuppression may accelerate the effect of HPV in malignant transformation of the epithelium as postulated by Roura *et al.* (2016).

2.6.2 Duration and use of combined oral contraception

In a study done by Moreno *et al.* (2002) with the tittle: The European Prospective Investigation into Cancer and Nutrition (EPIC) to follow up a cohort of 300 000 women over 9 years it was shown that the odds of the development of ICC increased with the duration of being on combined oral contraceptives (Moreno *et al.*, 2002). In a case-control study set in Ethiopia women who were on oral contraceptive were almost three times more likely to develop precancerous lesions of the cervix than non-users AOR=2.74, 95% CI: (1.6-7.4) p= <0.05 (Taye, Mihret and Muche, 2021).

2.7 Clinical risk factors

2.7.1 Duration on antiretroviral therapy

Not being on ART increased the likelihood of developing cervical precancer by more than twice in WLHIV; this was observed in a cross-sectional study of 454 HIV infected women (AOR= 2.31, 95% CI: [1.23-4.39] p= 0.026) (Lemu *et al.*, 2021). Being on ART restores the immune function therefor thought to reduce the acquisition of HPV by the cervical epithelium and promoting the clearance of HPV from the genital tract (Lemu *et al.*, 2021). Liu *et al.* (2018) in their systematic review of publications on HPV infection, precancerous lesions of the cervix and ICC in WLHIV stated that ART restores and maintains the immune function thereby reducing the effects of HPV on cervical epithelium. They also observed that with ART, HPV infection on the cervical epithelium reduced, cervical clearance of HPV increased with often regression of precancerous lesions (Liu *et al.*, 2018).

2.7.2 HIV Viral Load

HIV is associated with enhanced HPV acquisition, reduced clearance of HPV and the development of precancerous lesions, WLHIV with elevated HIV viral loads had three times the risk of acquiring HPV when compared to HIV negative women (Lemu *et al.*, 2021). Liu *et al.* (2018) goes on to state that HPV acquisition was higher with increasing HIV viral loads.

2.7.3 HPV Vaccination

Vaccinating adolescent girls aged 9 to 14 years is the most effective long-term intervention to reduce the development of ICC, high vaccination coverages protect the unvaccinated through herd immunity (WHO, 2020). A comparative modelling analysis in 78 LI and LMICs showed a reduction in ICC cases diagnosed from 18 per 100 000 to 2.1 per 100 000 which is a 98.4% reduction in cases over the next century (Brisson *et al.*, 2020). This was when girls only were vaccinated without even screening for cervical cancer which translated to 61 million cases averted (Brisson *et al.*, 2020). However only 30% of the eligible young girls live in the countries which have introduced the vaccine (Stelzle *et al*., 2020). Namibia is one of those countries which have not yet introduced mass HPV vaccination in the public sector (Korn *et al*., 2022).

2.8 Sociodemographic risk factors

2.8.1 Age

Age is a risk factor for the development of precancerous lesions of the cervix in WLHIV as shown below by exploring different studies in different settings. In a cross-sectional study in Amhara Ethiopia when investigating the prevalence of precancerous lesions and associated risk

factors in WLHIV it was noted that age greater than 30 was associated with the development of precancerous lesions (Belayneh, Mitiku and Weldegebreal, 2019). However; in two cross-sectional studies one from Namibia and one from Botswana it was noted that in both studies WLHIV under 25years of age had higher positivity rates than their older counterparts (Korn *et al.*, 2022; Ramogola-Masire *et al.*, 2022).

2.8.2 Level of education

According to WHO (2020) In the world's poorest countries the annual number of ICC cases is expected to increase from about 300 000 to 400 000 by 2030; the most affected will be the young undereducated women. Education is recognized as a significant risk factor to the development of ICC, below is a study which illustrates that it is also a risk factor for the development of precancerous lesions of the cervix in WLHIV. A level of education at college and above was seen as protective against the development of cervical precancerous lesions in a hospital-based case-control study of 200 women in Ethiopia, these women were 71% less likely to develop precancerous lesions compared to their counterparts (Taye, Mihret and Muche, 2021). Taye, Mihret and Muche (2021) postulate that higher education presents better employment opportunities which lead to greater autonomy when dealing with sexual and reproductive issues.

2.8.3 Sex work

Globally women who sell sex have a high prevalence of high-risk HPV infections attributable to multiple exposures; in sub–Saharan Africa this when combined with the HIV pandemic and the scarcity of quality screening and treatment facilities puts them at a high risk of developing precancerous lesions (Macleod and Reynolds, 2021). In Uganda where 719 female sex workers

of median age of 30 years were enrolled in a cross-sectional study and 6% (n=40) were VIA positive, the VIA positivity was more likely in women who reported having >100 lifetime partners (Namale *et al.*, 2021).

2.9 Behavioral risk factors

2.9.1 Multiple sexual partners

Several publications made in SSA have shown that multiple sexual partners are a risk factor for the development of precancerous lesions of the cervix as shown below. Women from three regions in Eswatini were enrolled in a cross-sectional study where they underwent VIA screening, women with two or more sexual partners were three times more likely to screen VIA positive than those with only one (Jolly *et al.*, 2017). The above findings were also supported by Belayneh, Mitiku and Weldegebreal (2019); in their study women with one sexual partner were 98% less likely to develop precancerous lesions of the cervix when compared to those having two or greater (AOR=0.112, 95% CI: [0.029–0.478] p= 0.003). Taye, Mihret and Muche, (2021) conducted a hospital-based case control study which showed that the odds of developing precancerous lesions were three times higher among women with multiple sexual partners than those in monogamous relationships, they postulated that this could be due to multiple exposures to HPV.

2.9.2 Early sexual debut

Early age of first sexual encounter and early age of first pregnancy are interrelated in most developing countries; the risk of developing cervical cancer was more than twice in those who had first intercourse and first pregnancy before the age of 16 years compared to those who had both after 21 years (Louie *et al.*, 2009) . Louie *at al.* (2009) postulated that the relationship

between cervical cancer and early first sexual encounter and child birth could be due to hormonal influences on the cervical epithelium and the immature cervix of the host. These findings were also partly corroborated by the outcomes of the study of (Kassa et al. (2019) conducted in Ethiopia where the age at first child birth (i.e., at age less than 18 years) was significantly associated with the development of pre-cancerous lesions of the cervix.

2.9.3 Sexually transmitted disease

Kassa *et al.* (2019) explored the relationship between sexually transmitted infections (STI) and the development of precancerous lesions of the cervix in WLHIV; in this study having an STI increased the likelihood of developing precancerous lesions of the cervix by 4-fold (AOR=4.04, 95% CI: [2,19-7.44]). It is postulated that co-infection with other STIs potentiates the effects of HPV on the female genital tract increasing the likelihood of developing precancerous lesions of the cervix (Kassa *et al.*, 2019). Weldegebreal and Worku (2019) from their systematic review support the view of Kassa *et al.* (2019) and state that any condition causing ulceration or inflammation to the genital tract is a predisposing factor to the development of precancerous lesions of the cervix. An individual can be simultaneously infected with several STIs including HPV. Suehiro *et al.* (2021) in a cross-sectional study to investigate the prevalence of HPV realized that 14% of participants who tested positive for HPV also had other STIs namely *Chlamydia trachomatis, Neisseria gonorrhoeae, Treponema pallidum.*

2.9.4 Smoking and tobacco use

The International Agency for Research on Cancer (IARC) in 2004 classified tobacco smoking as another cause of cervical cancer; it used pooled data from eight case control studies which

observed excess risk to the development of squamous cell carcinoma in active and ex-smokers (Ono *et al.*, 2019). Partners of male smokers may also be at higher risk of developing precancerous lesions and cancer; it was also noted that male smokers are at an increased risk of any HPV infection including high risk HPV infection, with which they can potentially infect their sexual partners (Ono *et al.*, 2019). Women who smoked were five times more likely to test VIA positive than those who did not in a cross-sectional study from Gabon (OR = 5.47, 95% CI: [2.60–11.52] p=<0.001) (Woromogo *et al.*, 2021).

2.10 Summary of literature review

The variations in prevalence for cervical precancerous lesions on WLHIV in SSA are due to different intensities of pressures like the HIV burden and the availability or lack of quality prevention, screening and treatment facilities in different countries in SSA (Kuguyo *et al.*, 2017; Nkfusai *et al*., 2019). Through the literature review it was demonstrated that there is an association between the psychosocial, behavioral, clinical and sociodemographic risk factors in different settings in and around SSA. The nature of the above-mentioned relationship was not known in the study population at Katima Mulilo ART clinic, this study was conducted to demonstrate the nature of this relationship.

CHAPTER 3: METHODOLOGY

3.1 Study setting and population

Namibia is a middle income Southern African country (MIC) with a population of just above two million people (Namibia Census, 2011) (MoHSS and ICFI, 2014). Katima Mulilo, where Katima Mulilo ART clinic is located is a district in the Zambezi region of Namibia (MoHSS and ICFI, 2014). The projected population for the Zambezi region for 2020 was 105 706 people of whom 50.9% were female. This region also has the highest HIV prevalence in Namibia (estimated at 22%) (MoHSS, 2019).

According to the MoHSS (2018) guidelines, VIA is supposed to be carried out in women who are aged 20 to 49 years, therefore the population studied was aged from 20 to 49 years of age. The VIA procedure is more cost effective for mass screening in LMICs and has acceptable sensitivity in this age group. However, it is important to note that post-menopausal women are screened using Pap smear due to lower sensitivity of VIA in this age group (WHO, 2017).

Inclusion criteria: The current study population was also defined geographically as women within 20 to 49 years who were living with HIV in the Katima Mulilo district of the Zambezi region of Namibia. These women were receiving health care at the Katima Mulilo ART clinic. The women had to have a uterus and cervix and should have undergone cervical cancer screening using the visualisation of the cervix under acetic acid technique (VIA). The VIA screening should have been performed on any of the women's routine visits within the period of July 2019 to July 2021. They should also have had penetrative vaginal sexual intercourse with a penis at least once in their lifetime; this is because HPV is a sexually transmitted infection which can be transmitted through genital skin to skin contact with someone who has

it therefore, most women become infected with HPV at or soon after their first penile vaginal sexual encounter (Palefsky, 2009).

Exclusion criteria: Women who would have had cervical cancer screening by any other method which is not VIA like Papanicolaou smear as these have different sensitivities (MoHSS, 2018). Women who had different or abnormal cervical anatomy than a normal women's cervix; for the VIA screen to be performed, the whole cervix has to be visualized, this may not be possible if the cervix has altered anatomy (MoHSS, 2018). Women who have had a total hysterectomy, as this procedure also removes the cervix (MoHSS, 2018). Women will be excluded if they were not born as female, like a trans gender individual who identifies as a woman but has male genitalia. Women who presented for rescreening after having had a previously abnormal result. Finally, we excluded women who were younger than 20 years and those older than 49 years, in accordance with the VIA screening guidelines for WLHIV in Namibia (MoHSS, 2018).

3.2 Study design

This was an observational cross-sectional study. This research design was preferred as it was able to fulfill the aim of measuring the prevalence of cervical precancerous lesions (outcome) as well as its associated risk factors (exposure) simultaneously. For instance, Sedgwick (2014) argued that a cross- sectional study when conducted can be used to measure the outcome and exposure(s) concurrently. This design is also logistically cheap when compared to other study designs such as the cohort studies, which take a long time and need more resources to follow up patients (Sedgwick, 2014). Patients were only interviewed once, as such, there was no need for follow up. This was particularly helpful as the study took place during the height of the Covid-19 epidemic in Namibia when there were lockdown restrictions to prevent population

movement. During the interviews, the Covid-19 prevention measures were adhered to as prescribed by the Namibian MoHSS. Data which could not be collected using questionnaires during interviews was collected retrospectively from clinic records as outlined below.

3.3 Sampling strategy

At Katima Mulilo ART clinic all women who have had cervical cancer screening also had their details documented in the facility cervical cancer register. In selecting the sample of participants for the intended research, a simple random selection method was used to generate a list of eligible patients who met the inclusion criteria from the facility cervical cancer screening register. On the list, each eligible patient file was assigned a random number generated during the participant selection process. The randomly selected participants who consented were enrolled in the study until the desired sample size was reached. The method of simple random selection was used as it was best to give an equal chance of selecting each participant, therefore there was a minimal chance of selection bias. This therefore allowed for greater generalizability of the study outcomes to the larger population of Katima Mulilo who attend the ART clinic and other similar populations (Bruce, Pope and Stanistreet, 2008). This method was also the least complex form of sampling; therefore, it offered the lowest chance of systematic errors.

3.4 Sample size calculation

The sample size was calculated using the formula below by Pourhoseingholi, Vahedi and Rahimzadeh, (2013): $\mathbf{n=Z^2\ P(1-P)/d^2}$: Where n= sample size, Z=level of confidence. 95% level of confidence which corresponded to 1.96 was used, P=prevalence of cervical pre-cancerous lesions in Sub Saharan Africa as estimated by Weldegebreal and Worku (2019) for HIV

positive women at 25.6%. d= effect size. An effect size of 5% was used. Therefore n= 1.96 x 1.96 x 0.256(1-0.256)/0.05x0.05 =3.8416 x 0.256(0.744)/0.0025 = 292.6

Since the proposed study was done on vulnerable individuals who sometimes refuse to participate and data was thought to be incomplete in some record sources, oversampling was done and as such, a total sample of 330 participants was proposed, an excess of 10% of the calculated sample catering for nonresponse. Due to the Covid-19 pandemic patients were given multi-month supplies of medication and other facility decongestion measures were implemented like ART home delivery, enrollment took very long and was stopped when the sample size reached 300 participants.

The data collection was completed in January 2022 at that time the document we referred to for the estimate for the prevalence of precancerous lesions of the cervix in WLHIV in SSA was from Weldegebreal and Worku (2019). However; in February 2022 a document by Korn *et al.* (2022) was released this document estimates the prevalence of precancerous lesions of the cervix in WLHIV in Namibia to be 17%. When the sample size is calculated using the formula by Pourhoseingholi, Vahedi and Rahimzadeh, (2013): $\mathbf{n=Z^2\ P(1-P)/d^2}$ and P=prevalence of cervical pre-cancerous lesions in Sub Saharan Africa as estimated by Korn *et al.* (2022) for HIV positive women at 17% then n=216.8. Because the document by Korn *et al*. (2022) was not available to us before February 2022, the sample size of 300 was used based on the document by Weldegebreal and Worku (2019).

3.5 Data collection and procedure

The three data collection tools were a cervical cancer screening and treatment program register (CCSTPR), the patient care booklet (PCB) and a structured questionnaire (SQ). These three

data sources were used to collect the reproductive, clinical, behavioral and sociodemographic variables to see if they were associated with the outcome variables. From the CCSTPR the outcome variables to be collected were either VIA positive or negative results (outcome), the family planning method and parity. The cervical CCSTPR also has the unique ART number for the patient who were screened, with the unique ART unique number also recorded in the PCB in the facility. This was used to link outcomes of the patients to the clinical information like the latest viral load and the duration the patient was on ART. Finally, an SQ (See Appendix I) was used to collect the other variables like the number of lifetime sexual partners, age at sexual debut, marital status, age at first marriage, history of sexually transmitted infections (STIs), the highest level of education, HPV vaccination history, employment status and use of tobacco.

3.6 Data analysis

Raw data on exposure and outcome variables captured from SQs, CCSTPR registers and PCBs was collected and categorized into an Excel (2013) spreadsheet (Appendix II). This data was analyzed using IBM SPSS statistical package (version 28) after being exported from the Excel file. Descriptive statistics like frequencies, percentages, and standard deviations were used to describe the data. Data on VIA positivity was analysed to determine the overall prevalence precancerous lesions, it was then presented in tables according to sociodemographic, clinical, behavioral and reproductive risk factors. A Chi-square test was conducted to determine if there were significant differences between the VIA positive and negative groups. Binomial logistic regression analysis was conducted to determine the associations between VIA positivity and sociodemographic factors, behavioral, clinical and reproductive factors. The association was then assessed using the adjusted odds ratio, confidence intervals which did not overlap and p values <0.05 were considered significant.

3.7 Outcome validity

The extent to which a survey or instrument is able to give a true result or is able to measure what it is intended to measure is the validity, this is significant if the results of the study are to be generalised to a larger population (Health Knowledge, 2022). Face validity can refer to the unambiguity or clarity of a tool, in this instance the structured questionnaire, one way to ensure this is to do a pilot test of the SQ on a sample of the intended respondents to see if comprehension is easy (Bruce, Pope and Stanistreet, 2008). The unambiguity or clarity of the SQ, was pretested on small sample of participants in similar conditions as the ones where the study participants were going to be interviewed. The results from the test group were analysed to ensure that the information captured was relevant to the study being conducted.

3.8 Reliability

Reliability is the ability to produce similar results under similar conditions at different times (Health Knowledge, 2022). To reduce variation a standardized structured (SQ) data collection tool was used, this ensured that data was collected in a similar manner for each respondent. One trained assistant conducted all the interviews this was hoped to observer variation where inconsistency would have been likely if more than one person administered the questionnaire (Bruce, Pope and Stanistreet, 2008).

3.9 Limitations

Cervical cancer screening is offered to women who present for ART care at Katima Mulilo ART clinic, therefore the study sample may not have been representative of all the HIV positive women in this area since it excluded those who may have been HIV positive and not present

for ART care. The results may also not be generalizable to the larger Katima Mulilo community due to the fact that VIA screening is optional, therefore the women who decline VIA services may have different characteristics to those who consent to the procedure. The proposed facility is located in the most urban part of the Zambezi region of Namibia and the rest of the region is rural therefore results from this study may not be fully representative of the HIV positive women in the region. The data is collected at one point in time; as such, it will be difficult to infer a causal relationship between identified risk factors and the outcome variable or establish a trend in cervical pre-cancer outcomes over time as this is a cross sectional study.

3.10 Ethical considerations

For ethics approval the soundness of the research was assessed by the Community and Health Sciences Faculty and Senate Committee Higher Degrees. On approval from the higher degrees committee, the ethics clearance to conduct research was obtained from the University of the Western Cape's Biomedical Research Ethics Committee (Appendix III). When the approval was awarded, an application was then made to the Namibian Biomedical Research Ethics Committee (BREC) and Research Management Committee which are under the Namibian Ministry of Health and Social Services in the office of the Executive Director (Appendix V). After approval was granted by the Research Management Committee (Appendix IV), formal permission was sought to conduct the study from the Zambezi Regional Health directorate and the Katima Mulilo ART clinic.

Participants who met the inclusion criteria were invited to take part in the study and were asked to sign an informed consent. They were informed that participation was voluntary and that they were free to withdraw from the study at any point in time, with refusal or withdrawal from

participation bearing no consequences including affecting their health care at any MoHSS facility in Namibia. The participants were informed that there was no remuneration of any kind before during and after participating in the study. Participants were provided with an information sheet which had all this information and detailed information on the aim of the study, the data collection procedures and how the results of the study would be used. This information was conveyed in a language the participants fully comprehended. On this information sheet the contact details of the investigator and the people of authority were provided in case the participants needed to seek clarity or lodge a complaint on matters relating to the proposed study. Participants were also encouraged to ask questions for clarification before signing the consent forms and at any time during the interviews. Participants were asked permission to use their stored information in the CCSTPR and PCB. To ensure the confidentiality, participants were interviewed in a secured and private office provided in the clinic. To maintain anonymity identification numbers were assigned to participants and none of their identifying details were used. The participant records containing data form the CCSTPR, PCB and SQ were stored in a locked cabinet in the researcher's office where access was restricted to the primary researcher only. Electronic data was stored on the researcher's personal computer and this was password protected. Data generated from this research will be kept for five years after which electronic files will be deleted and paper-based information will be incinerated. The research findings shall be shared with the UWC School of Public Health and the Namibian Biomedical Research Ethics Committee (BREC) and Research Management Committee which are under the Namibian Ministry of Health and Social Services in the office of the Executive Director.

CHAPTER 4: RESULTS

4.1 Introduction

Table 3. The study findings for the cross-sectional study are described below.

VIA screening result	Frequency and percentage
VIA Negative	241 (80.3%)
VIA Positive	59 (19.7%)
Total	300 (100%)

Of the 300 women aged 20 to 49 years screened 59 tested VIA positive giving a yield of 19.7%. While 80.3% tested VIA negative.

Table 4. Sociodemographic characteristics

Age range in years	Frequency and percentage	VIA test result		Chi-Square test	P-value
		VIA+ve	VIA-ve		
20-25	27 (9.0%)	6 (22.2%)	21 (77.8%)	2.178	0.703
26-31	34 (11.3%)	7 (20.6%)	27 (79.4%)		
32-37	71 (23.7%)	13 (18.3%)	58 (81%7%)		
38-43	99 (33.0%)	23 (23.2%)	76 (76.8%)		
44-49	69 (23.0%)	10 (14.5%)	59 (85.5%)		
Marital status	**Frequency and percentage**	**VIA test result**		**Chi- Square test**	**P-value**
		VIA+ve	**VIA-ve**		
Single	93 (31.0%)	21 (22.6%)	72 (77.4%)	1.743	0.418
Married	140 (46.7%)	23 (16.4%)	117 (83.6%)		
Divorced	67 (22.3%)	15 (22.4%)	52(77.6%)		
Highest Educational qualification	**Frequency and percentage**	**VIA test result**		**Chi-Square test**	**P-value**
		VIA+ve	**VIA-ve**		
Primary	165 (55.0%)	33 (20%)	132 (80%)	2.150	0.357
Secondary	116 (38.7%)	20 (17.2%)	96 (82.8%)		
University/college	19 (6.3%)	6 (31.6%)	13 (68.4%)		
Commercial Sex Work	**Frequency and percentage**	**VIA test result**		**Chi-Square test**	**P-value**
		VIA+ve	**VIA-ve**		
Yes	0 (0%)	--	--		
No	300 (100%)	59 (19.7%)	241 (80.3%)		

Table 4 above shows the WLHIV who were screened according to their sociodemographic characteristics. The highest proportion screened was the women in the age group range of 38 to 43 years (33%) while the lowest proportion were the women aged 20 to 25 years old (9%). The majority of the women were married at 46%, the second largest group to be screened were women who were single 31% then the divorced women only comprised of 22% of the population. The majority of the women only had primary school education with the least proportion of women having had attained college or university education.

When comparing the women who tested VIA positive and those who tested VIA negative using the Chi-square test and the Fisher's exact test according to age groupings, marital status and highest educational qualification attained, there were no significant differences between the two groups.

Table 5. Clinical characteristics

Duration on ART in years	**Frequency and percentage**	**VIA test result**		**Chi-square test**	**P-value**
		VIA+ve	**VIA-ve**		
<5 Years	62 (20.7%)	21(33.1%)	41 (66.1%)	9.980	0.002
>5 Years	238 (79.3%)	59 (19.7%)	200 (84%)		
Latest Viral Load Result in copies/ml	**Frequency and percentage**	**VIA test result**		**Fisher's Exact test**	**P-value**
		VIA+ve	**VIA-ve**		
<1000	289 (96.3%)	53 (18.3%)	236 (81.7%)		0.009
>1000	11 (3.7%)	6 (54.5%)	5 (45.5%)		
Vaccinated against HPV	**Frequency and percentage**	**VIA test result**		**Chi-square test**	**P-value**
		VIA+ve	**VIA-ve**		
Yes	0 (0%)	--	--		
No	300 (100%)	241 (19.7%)	59 (80.3%)		
History of STI	**Frequency and percentage**	**VIA test result**		**Chi-square test**	**P-value**
		VIA+ve	**VIA-ve**		

Yes	31 (10.3%)	8 (25.8%)	23 (74.2%)	0.825	0.473
No	269 (89.7%)	51 (19.0%)	218 (81.0%)		

According to Table 5 above, when the WLHIV were described according to their clinical characteristics; the majority had been of ART for more than 5 years while only 20.7% had been on ART for less than five years. The majority of the WLHIV who were on ART had viral suppression, their viral loads were less than 1000 copies/ml (96.3%). A very small proportion of the women were having a viral load of greater than 1000 copies/ml (3.7%). Of the women who were screened 10.3% reported as having been treated for a sexually transmitted infection (STI), however from the SQ information none of them knew the kind of STI they had, they only knew that they had been treated for a STI in general. None of the WLHIV screened for cervical precancerous lesions were vaccinated against HPV.

There were significant differences between the women who tested VIA positive and those who tested VIA negative when the women were grouped according to duration on ART and the latest viral load result ($\chi 2 = 9.98$, $p = 0.002$) and (Fishers exact test two-tailed $p = 0.009$), respectively. There was no significant difference when the Chi-square test was used to compare VIA positivity between women who had a history of a STI and those who did not.

Table 6. Reproductive characteristics

Parity	**Frequency and percentage**	**VIA test result**		**Chi-square test**	**P-value**
		VIA+ve	VIA-ve		
0 children	24 (8%)	2 (8.3%)	22 (91.7%)	4.14	0.123
1-3 children	208 (69.3%)	47 (22.6%)	161 (77.4%)		
4+ children	68 (22.7%)	10 (14.7%)	58 (85.3%)		
Family planning	**Frequency and percentage**	**VIA test result**		**Fisher's Exact test**	**P-value**
		VIA+ve	VIA-ve		
None	232 (77.3%)	40 (17.2)	192 (82.8)		0.166

Oral	10 (3.3%)	3 (30.0)	7 (70.0%)		
Injectable	52 (17.3%)	14 (26.9)	38 (73.1)		
Condom	6 (2.0%)	2 (33.3)	4 (66.7)		

Table 6 shows the women who were screened using the VIA method when classified according to reproductive characteristics. The majority of the women had between one and three children while 8% of them did not have any children at all at the time of screening while 22.7 % of the women had four children and above. The majority of the women did not use any family planning method (77%), while 17.3% used injectable forms of family planning and only 2% used a condom.

When comparing the VIA positivity according to parity using the chi-square test there were no significant difference between the two groups. Using the Fisher's exact rule there were also no differences in VIA positivity between the two groups according to family planning methods among the WLHIV.

Table 7. Behavioral characteristics

Lifetime sexual partners	**Frequency and percentage**	**VIA test result**		**Chi-square test**	**P-value**
		VIA+ve	**VIA-ve**		
1 partner	110 (36.7%)	16 (14.5%)	94 (85.5%)	15.279	<0.001
2-3 partners	100 (33.3%)	13 (13.0%)	87 (87.0%)		
4+ partners	90 (30.0%)	30 (33.3%)	60 (66.7%)		
Age at first sexual debut in years	**Frequency and percentage**	**VIA test result**		**Chi-square test**	**P-value**
		VIA+ve	**VIA-ve**		
<16	33 (11.0%)	19 (57.6%)	14 (42.4%)	33.727	<0.001
16+	267 (89.0%)	40 (15.0%)	227 (85.0%)		
Age at 1st marriage in years	**Frequency and percentage**	**VIA test result**		**Chi-square test**	**P-value**
		VIA+ve	**VIA-ve**		
<18	39 (13.0%)	17 (43.6%)	22 (56.4%)	20.089	<0.001
18+	168 (56.0%)	21 (12.5%)	147 (87.5%)		

Not married	93 (31.0%)	21 (22.6%)	72 (77.4%)		
Tobacco use	**Frequency and percentage**	**VIA test result**		**Fisher's Exact test**	**P-value**
		VIA+ve	**VIA-ve**		
Active smoker	9 (3%)	3 (33.3%)	6 (66.7%)		0.537
Stopped smoking	7 (2.3%)	1 (14.3%)	6 (85.7%)		
Never smoked	284 (94.7%)	55 (19.4%)	229 (80.6%)		

According to Table 7 above, the majority of the women screened (36%) had only one lifetime sexual partner followed by those who had two to three partners and 30% had four or more sexual partners at the time of screening. One in ten women had their first sexual debut at the age below sixteen years, while 89% had their first sexual debut at sixteen years and above. A little more than half of the women (56%) were married at 18 years and above while thirteen percent (13%) were married when they were below the age of 18 years. About a third (31%) of the women were not married at the time of screening. A vast majority of the women had never smoked (94%) while 2.3% had stopped smoking and only nine women (3%) were actively smoking.

There were significant differences between WLHIV who tested VIA positive and those who tested negative when grouped according to number of sexual partners, age at first marriage and first sexual debut ($\chi^2 = 15.279$, p = 0.001, $\chi^2 = 20.809$ p = 0.001 and $\chi^2 = 33.727$ p = 0.001, respectively). There was no significant difference in VIA positivity in WLHIV classified according to smoking status.

Table 8. Binary logistic regression analysis showing the association between VIA positivity and sociodemographic risk factors

	Unadjusted Odds Ratio			**Adjusted Odds Ratio**		
	Crude OR	**95% CI**	**p-value**	**AOR**	**95% CI**	**p-value**

Age range	20-25	Ref			Ref		
	26-31	0.907	0.265-3.106	0.877	1.845	0.360-9.450	0.462
	32-37	0.784	0.264-2.330	0.662	0.895	0.215-3.716	0.878
	38-43	1.059	0.382-2.938	0.912	2.205	0.545-8.917	0.268
	44-49	0.593	0.192-1.833	0.364	1.422	0.318-6.360	0.645
Marital status	Single	Ref			Ref		
	Married	0.674	0.348-1.305	0.242	2.070	0.678-6.321	0.201
	Divorced	0.989	0.466-2.099	0.977	1.891	0.601-5.952	0.276
Highest level of education	Primary	Ref			Ref		
	Secondary	0.833	0.451-1.541	0.561	0.658	0.302-1.433	0.292
	Tertiary	1.846	0.653-5.222	0.248	3.060	0.851-10.999	0.087

Crude OR: unadjusted odds ratio; AOR: adjusted odds ratio for all the variables measured

According to Table 8 above there were no associations between VIA positivity and the sociodemographic risk factors (i.e., age, marital status and highest level of education achieved) in WLHIV screened, both before and after adjusting for all the confounding variables.

Table 9. Binary logistic regression analysis showing the association between VIA positivity and clinical risk factors

		Unadjusted Odds Ratio			Adjusted Odds Ratio		
		Crude OR	95% CI	p-value	AOR	95% CI	p-value
Duration on ART	<5 years	Ref			Ref		
	>5 years	0.371	0.198-0.697	0.002	0.366	0.177-0.755	0.007
Latest viral load results	<1000	Ref			Ref		
	>1000	5.343	1.572-18.165	0.007	2.804	0.685-11.488	0.152
History of STI	Yes	Ref			Ref		
	No	0.673	0.285-1.590	0.366	1.488	0.472-4.692	0.498

Crude OR: unadjusted odds ratio; AOR: adjusted odds ratio. OR for Duration on ART was adjusted for = Parity, Number of lifetime sexual partners, Age at sexual debut and Age at first marriage. OR for Latest viral load results were adjusted for = Duration on ART, Parity, Lifetime sexual partners, Age at sexual debut and age at first marriage

After binary logistic regression analysis to measure the strength of association between clinical risk factors and VIA positivity, being on ART for more than five years was seen to be protective from developing precancerous lesions of the cervix (Table 9). The Adjusted Odds Ratio was 0.366 with a 95% CI: (0.177-0.755) this finding was statistically significant p= 0.007 after adjusting for parity, number of lifetime sexual partners, age at sexual debut and age at first

marriage. Having a viral load which is above 1000 copies/ml was seen to increase the likelihood of developing precancerous lesions of the cervix by more than five times compared to women with a viral load less than 1000 copies/ml (OR=5.343, 95% CI: [1.572-18.165], p=0.007). However; after adjusting for duration on ART, parity, lifetime sexual partners, age at sexual debut and age at first marriage AOR=2.084, 95% CI: [0.685-11.488] the relationship between latest viral load and the development of precancerous lesions of the cervix was no longer statistically significant p=0.152.

Table 10. Binary logistic regression analysis showing the association between VIA positivity and reproductive risk factors

		Unadjusted Odds Ratio			Adjusted Odds Ratio		
		Crude OR	**95% CI**	**p-value**	**AOR**	**95% CI**	**p-value**
Parity	0 children	Ref			Ref		
	1-3 children	3.211	0.728-14.157	0.123	4.209	0.832-21.293	0.082
	4+ children	1.897	0.385-9.352	0.432	2.165	0.345-13.587	0.410
Family Planning	None	Ref			Ref		
	Oral	2.057	0.510-8.298	0.311	2.600	0.490-13.791	0.262
	Injectable	1.768	0.877-3.565	0.111	1.350	0.544-3.350	0.518
	Condom	2.400	0.425-13.554	0.322	1.832	0.206-16.250	0.587

Crude OR: unadjusted odds ratio; AOR: adjusted odds ratio for all the variables measured

According to Table 10 above, there was no association between reproductive risk factors (parity and family panning method) and VIA positivity in WLHIV screened for the current study, both before and after adjusting for all the confounding variables.

Table 11. Binary logistic regression analysis showing the association between VIA positivity and behavioral risk factors

	Unadjusted Odds Ratio			Adjusted Odds Ratio		
	Crude OR	**95% CI**	**p-value**	**AOR**	**95% CI**	**p-value**

Lifetime sexual partners	1 partner	Ref			Ref		
	2-3 partners	0.878	0.399-1.930	0.746	0.719	0.304-1.700	0.452
	4+ partners	2.937	1.477-5.844	0.002	2.797	1.302-6.009	0.008
Age at sexual debut	<16	Ref			Ref		
	16+	0.130	0.060-0.280	<0.001	0.212	0.082-0.547	0.001
Age at first marriage	<18	Ref			Ref		
	18+	0.185	0.085-0.404	<0.001	0.310	0.114-0.841	0.021
	Not married	0.377	0.170-0.838	0.017	0.517	0.196-1.364	0.183
Tobacco use/smoking	Active	Ref			Ref		
	Stopped	0.333	0.027-4.186	0.395	0.578	0.030-11.125	0.716
	Never used	0.480	0.116-1.981	0.310	0.540	0.095-3.074	0.487

Crude OR: unadjusted odds ratio; AOR: adjusted odds ratio. OR for Lifetime sexual partners adjusted for = Duration on ART, Parity, Age at sexual debut, Age at first Marriage. OR for Age at sexual debut adjusted for = Duration on ART, Parity, Lifetime sexual partners, Age at first marriage. OR Age at first marriage adjusted for = Duration on ART, Parity, Lifetime sexual partners, Age at sexual debut

Table 11 above shows the results from the binary logistic regression to assess the association between behavioral risk factor and VIA positivity. There was a significant association between having four or more lifetime sexual partners and VIA positivity. The adjusted odds of developing cervical precancerous lesions were almost three times greater in women who had four or more sexual partners than those who only had only one AOR= 2.797, 95% CI: [1.302-6.009], and the outcomes were statistically significant p=0.008. Sexual debut was another risk factor which had a significant association with VIA positivity. In this case, those women who had their first sexual debut at ages 16 years and older had lower odds of developing precancerous lesions compared to those who had their first sexual debut when they were younger than 16 years (AOR=0.212, 95% CI: [0.082-0.547], p=0.001). Being married at an older age i.e., 18 years and older was protective of developing precancerous lesions of the cervix (AOR=0.310, 95% CI: [0.114-0.841], p=0.021). Initially not being married seemed to be protective of developing precancerous lesions of the cervix (OR=0.377, 95%CI: [0.170-0.838], p=0.017). However, after removing the confounding effects of the duration on ART, parity, lifetime sexual partners and age at sexual debut the outcome was no longer significant (AOR=0.212, 95% CI: [0.196-1.364], p=0.183).

4.2 Summary of findings

In this study three hundred WLHIV aged between twenty to forty-nine were screened for cervical cancer using the VIA method. The VIA positivity was 19.7%. From the results of logistic regression analysis women who were on ART for longer than five years, married at 18 years and above, and those that had their first sexual debut when they were 16 years and older were less likely to develop precancerous lesions of the cervix. From the same study having four or more sexual partners was associated with a higher risk of developing precancerous lesions of the cervix.

The crude odds ratios for the associations between age, marital status, highest level of education, parity, family planning method, history of STI and tobacco smoking and the development of precancerous lesions of the cervix did not reach statistical significance with p-values being greater than 0.05. Removing the confounding effects of other variables (such as age, marital status, highest level of education, duration on ART, latest viral load, history of STI, parity, family planning history, lifetime sexual partners, age at first marriage and tobacco use) did not change the adjusted odds ratio outcomes.

CHAPTER 5: DISCUSSION

5.1 Introduction

In the current study to determine the prevalence and risk factors for the development of precancerous lesions in WLHIV receiving health care at Katima Mulilo ART clinic in the Zambezi region of Namibia, the prevalence of cervical precancerous lesions was found to be 19.7%. The prevalence outcome for the current study is not very different from the program report for the first 18 months of the VIA cervical screening program for Namibia which looked at WLHIV who were screened which showed a prevalence of 17% (Korn *et al.*, 2022). The prevalence from this study is below the SSA estimate of 25.6% reported by Weldegebreal and Worku (2019) in their systematic review and meta-analysis. However, these authors further admit that the prevalence of cervical precancerous lesions has been estimated to range from as low as 2.9% to as high as 79% within the SSA region. Large variability in cervical precancerous lesion prevalence between different SSA countries and within the same country regions has been reported. For instance, in Northwest Ethiopia the prevalence in WLHIV was 17.8%, while in Northern Uganda it was 3%, whereas pooled data from three regions of Eswatini showed a prevalence of 22.9% (Getinet *et al.*, 2015; Izudi, Adrawa and Amongin, 2016; Jolly *et al.*, 2017). The variability in prevalence have also been noted within the borders of the same country. For example, different cross-sectional studies conducted within Ethiopia showed the prevalence outcomes that ranged from 9.9% to 18.7% (Belayneh, Mitiku and Weldegebreal, 2019; Lemu *et al.*, 2021).

Even though Kuguyo *et al.* (2017) emphasized that the often-high prevalence of cervical precancerous lesions and cervical cancer in SSA is due to poor cancer screening and treatment

access, another modifying factor to the prevalence in SSA is access to ART. Indeed Kelly *et al.* (2018) in their meta-analysis noted that compared to those not on ART, WLHIV on ART have lower prevalence of high-risk HPV and lower precancerous lesions of the cervix. In this research, the authors also presented outcomes of WLHIV on ART showing cervical precancerous lesions regression, or reduced likelihood of lesions progressing to ICC when compared WLHIV not on ART (Kelly *et al.*, 2018). Indeed; programmatic data on cervical cancer screening in Namibia showed that the prevalence for cervical precancerous lesions in WHLIV was 17% while for HIV negative women was at 15% (Korn *et al.*, 2022). In Namibia all the WHLIV screened were on ART and the national viral load suppression rate was at 92% in 2018, hence the close to equal spread of the findings between HIV positive and negative women (Korn et al., 2022). With the afore-presented findings, ART coverage should be taken into consideration as a strong modifier of the prevalence of precancerous lesions in different settings in SSA.

5.2 Sociodemographic risk factors

The sociodemographic risk factors were explored in terms of their role as risk factors in the development of precancerous lesions of the cervix. In this case, no significant differences were detected between those WLHIV who were VIA negative and those who were VIA positive. According to literature older age is usually identified as a common risk factor to the development of precancerous and cancerous lesions of the cervix (Makuza *et al.*, 2015; Belayneh, Mitiku and Weldegebreal, 2019; Woromogo *et al.*, 2021). However, it is worthwhile to note that some of the literature which is recently coming out mentions that in WLHIV precancerous lesions are more prevalent in younger women than older women (Korn *et al.*, 2022; Ramogola-Masire *et al.*, 2022). However, this may be a topic for further research. Korn *et al.* (2022) and Ramogola-Masire *et al.* (2022) using program data from Namibia and

Botswana have recently shown that women aged 20 years to 29 years have higher prevalence of cervical precancerous lesions than their older counterparts.

Using the chi-square test in the current study, there were no significant differences in VIA positivity among women according to their marital status. These outcomes seem to be contrary to the outcomes of studies conducted in different parts of Africa, where marital status has been shown to have a significant association with the development of precancerous lesions of the cervix. Makuza *et al*. (2015) on their a cross-sectional study for instance noted that, in Rwanda, being unmarried (single, divorced or widowed) increased the risk of developing precancerous lesions of the cervix when compared to being married. Obure *et al*. (2009) also found higher rates of cervical precancerous lesions in divorced, widowed and single women compared to married women. Even though in the current study we could not observe significant outcomes, the VIA positivity was higher among single and divorced women, than in married women (22.6% and 22.4% versus 16.4%).

From the current study majority of the women were found to have primary school education (55%), with few had post-secondary school education. This outcome is contrary to the outcomes of the 2013 demographic health survey (DHS) of Namibia, where few WLHIV (12.6%) had primary education, with the majority having attained secondary education with some progressed to have some post-secondary education in the Zambezi region (MoHSS and ICFI, 2014).

Education is recognized as a risk factor to the development of ICC in women. Corral *et al.* (1996) for instance, found that in Ecuador women with primary education had twice the risk

of ICC compared to those with secondary or higher education. In this research, illiterate women had almost six times the incidence. When looking at precancerous lesion data from Zambia's six provinces, it is shown that educational attainment is inversely associated with the diagnosis of abnormal cervical lesions in women screened for cervical cancer (Hamoonga *et al.*, 2017). Education has been found to contribute significantly to the development of ICC in other African settings. Singini *et al.* (2021) for instance, ranked education high among HIV positive women's the risk factors that contribute to ICC in black women in a Johannesburg study. In this case-control study, the researchers concluded that 16.9% of cervical cancers could have been prevented if the women participating in this research were educated up to secondary level and above (Singini *et al.*, 2021).

None of the women in the current study identified themselves as engaging in sex work. We are not sure of the validity of these outcomes, given the bias in response to such a question that is brought about by the fear of being stigmatized by the healthcare workers. Recent estimates of female sex workers (FSWs) in Katima Mulilo range from 453 to 800 (Wesson *et al.*, 2019). Moreover, the HIV prevalence in FSWs in Katima Mulilo is estimated to be to be 52.3%, while based on the current estimates only a third of FSWs in Namibia were on ART based on the countrywide survey (Jonas *et al.*, 2020). With the above observation stigma, exclusion and lack of access may have contributed to this study not having anyone who identified as a FSW despite the significant numbers in Katima Mulilo and the high HIV prevalence in this group.

5.3 Clinical risk factors

In this study WLHIV who had been on ART for more than five years were less likely to present with abnormal cervical lesions compared to those who had been on ART for less. This

significant finding is supported by several publications including a systematic review and meta-analysis by Kelly *et al*. (2018) which showed that high risk HPV incidence was lower among WLHIV who were on prolonged ART compared to those who were ART naive or on ART for less than 2 years. Liu *et al*. (2018) also showed in their systematic review and meta-analysis that ART reduces HPV types 16 and 18 incidence by up to 72%, and that being on ART increased the clearance of HPV infection from the genital tract and reduced the progression to cancer.

None of the women in the study had been vaccinated for HPV. This is because HPV vaccination has not yet been launched in the public sector in Namibia. However, HPV vaccination is available in the private sector (Korn *et al.*, 2022).

In the current study WLHIV with high viral loads were five times more likely to present with precancerous lesions of the cervix when compared with WLHIV whose viral loads were less than 1000c/ml. However; after adjusting for confounders (duration on ART, parity, lifetime sexual partners, age at sexual debut and age at first marriage) (AOR=2.084, 95% CI: [0.685-11.488], p=0.152) the relationship was no longer statistically significant.

Even though a little bit above one in ten women in the current study reported having had a STI before, they could not offer diagnosis on the type of STI they had, except that they highlighted that they had been informed by a health care worker after reporting symptoms. There was no significant association between STI history and precancerous lesions of the cervix in the current study. Sexually transmitted infection prevalence is difficult to determine when the syndromic diagnostic approach is used, as it is used in Namibia. This is because diagnosis through this

approach relies on symptoms as reported by the patient, unfortunately this approach is unreliable as most infections are asymptomatic (Francis *et al.*, 2014; MoHSS, 2021). That being said; literature does give evidence that STIs are significant risk factors to the development of precancerous lesions of the cervix. Indeed, Taye *et al*. (2021), Kassa *et al*. (2019) and Weldegebreal and Worku (2019) previously demonstrated the increased risk of developing precancerous lesions associated with STIs.

5.4 Reproductive risk factors

In the current study; when assessing the relationship between abnormal cervical lesions and reproductive risk factors (parity and family planning methods) among WLHIV there were no significant correlations observed. The majority of the women enrolled in the current study had at least one to three children (69.3%), those who had four and above were 22.7% with the lowest proportion having no children at all (8%). The findings from the study almost mirror the observations of the Namibian DHS conducted in 2013 that showed that the fertility average rate for women aged 15 to 49 years was 4.2, however this was almost ten years ago (MoHSS and ICFI, 2014). In different settings in SSA the relationship between parity and precancerous lesions of the cervix has been demonstrated and different theories have been brought forward. Belayneh *et al*. (2019) for instance, observed in a hospital sitting case-control study that having more than two children was a factor associated with the occurrence of precancerous lesions on the cervix. Belayneh *et al*. (2019) further postulated that the repeated trauma experienced during repeated vaginal deliveries exposes the genital wall to HPV. Another theory by Roura *et al.* (2016) in observations from a prospective cohort study which demonstrated a positive correlation between full term pregnancies with the development of abnormal cervical lesions points to hormonal influence. It is thought that the high estrogen and progesterone levels during pregnancy alter the epithelium covering the cervix, thereby exposing it to HPV facilitating

progression to precancer and eventually ICC (Roura *et al.*, 2016). Another theory is that the immune-suppression induced by pregnancy to potentially prevent host rejection of the fetus may facilitate unchecked HPV induced carcinogenesis (Roura *et al*.,2016). The systematic review by Weldegebreal and Worku (2019) with focus on WLHIV also concluded that WLHIV who had more than two births had almost twice the risk of developing precancerous lesions than those who had two full-term pregnancies and less.

According to the Namibian DHS of 2013 49.8% of women aged 15 to 49 years in Katima Mulilo were using contraceptives, 3.8% used the pill, 39.8% used injectables methods and 5.3% were using the male condom while 0.2% used the female condom (MoHSS and ICFI, 2014). From the population in the current study enrolled at Katima Mulilo ART clinic, 77.3% were not on any form of contraceptives, 3.3% used oral contraceptives, 17% were on injectable methods and 2% used condoms. It could be possible that the reason we could not find significant association between the contraceptive use and the occurrence of precancerous lesions was due to the low frequency of women who were documented as using combined oral contraceptives. When comparing the findings from the study and the Namibian DHS of 2013; there is very low use of contraceptives among women in Katima Mulilo. Findings from both sources show relatively high use of injectable forms of contraceptives. The data source used to collect the contraceptive use did not specify the kind of contraceptive used. It only defined it broadly like oral, injectable or condom. According to the MoHSS (2021); the oral contraceptives available in the public sector in Namibia are the combined oral contraceptive (COC) and the progesterone only pill (POP), these have varying hormonal concentrations according to brand. Moreover, there are also two types of injectables used in Namibia, of which are progesterone only depot medroxyprogesterone acetate and norethisterone enanthate

(MoHSS, 2021). It is also important to note that in the current study none of the women had implants or wore intrauterine contraceptive devices (IUCD).

Even through in the current study we could not find significant differences and associations between VIA positivity and family planning methods, there is available scientific evidence which suggests that contraceptives are risk factors in the development of precancerous lesions of the cervix and ICC (Moreno *et al.*, 2002). According to a systematic review and meta-analysis from 10 case-control studies for Asia, South America and Europe, Moreno *et al.* (2002) have long shown that the risk of ICC in women increased threefold if they are infected with HPV and had used oral contraceptives for five years of more. Loopik *et al.* (2020) also argue that, COC seem to promote the integration of high-risk HPV DNA into the host genome, where there is expression of HPV oncoproteins which enhance carcinogenesis Roura *et al.* (2016) on the other hand argue that, just as prolonged use of OCs increases the risk of developing precancerous lesions of the cervix, cessation of use is also associated with the reduction in the risk of developing precancerous lesions of the cervix and ICC.

5.5 Behavioral risk factors

When the women were grouped based on the number of their lifetime sexual partners, age at first sexual debut and age at first marriage, the Chi-square analysis showed significant differences in VIA positivity. There was also a significant likelihood of developing precancerous lesions of the cervix which was more pronounced with an increasing number of sexual partners. Being married at an older age and delaying sexual debut on the other hand was associated with a reduced likelihood of developing cervical precancerous lesions.

According to the DHS of 2013 in Katima Mulilo the age at first sexual intercourse for women was 18.1 years while in the study population with one in ten of the women participating in this survey had their first sexual intercourse when they were less than 16 years (MoHSS and ICFI, 2014). From the current survey, 13% of the women got married below the age of 18 years. According to the child marriage report of Namibia of 2020, the age of consent is 16 years however the act is not an offence if the partner is less than 3 years older than the minor and the age of marriage is 18 years (MGEPESW, UNICEF and UNFPA, 2020).

In fact, Louie *et al.* (2009) long stated that, age at first marriage has been used as a proxy to age at intercourse because early first marriage may likely lead to early pregnancy. Early first intercourse has also been linked to early acquisition of high-risk HPV. On the other hand, early sexual intercourse has been liked to risky sexual behaviours such as unprotected intercourse, multiple sexual partners and the woman's partner having multiple sexual partners (Loue *et al.*, 2009). In line with the results from the current study in Katima Mulilo, a retrospective case-control study conducted in Ethiopia managed to demonstrate that initiation of sexual intercourse before the age of 15 years increased the risk of developing cervical precancerous cervical lesions by up to 5.6 times (Kassa *et al.*, 2019).

Finally, in line with the Namibian DHS of 2013 that showed that only 4% of women aged 15-49 in Namibia smoked cigarettes, with older women tended to smoke more than younger women (MoHSS and ICFI, 2014). The current study also showed that only 3% of the participants were actively smoking at the time of the study. Even though no significant association between smoking and the development of precancerous lesions in the current study were observed, some SSA literature managed to elucidate this relationship through cross-

sectional studies conducted in Gabon and Nigeria (Durowade *et al.*, 2012; Woromogo *et al.*, 2021). To emphasize the risk conferred by tobacco; in a systematic review of cervical cancer prevention policies for WLHIV with specifications for SSA countries with the highest HIV prevalence, tobacco use warnings have been adopted in all the countries reviewed (Lem Asangbeh-Kerman *et al.*, 2021). Smoking may not have been a very strong risk factor for the development of cervical precancerous lesions since tobacco use in the current study as well as in Black African women is generally very low (3% and 4.1%) respectively (Singini *et al.*, 2021).

5.6 Limitations of the study

While the current study had many strengths that have been highlighted above, there are limitations that are worth noting when considering the study findings. Because the current study was cross-sectional; all measurements were conducted at a single point in time thus eliminating an opportunity to follow up (Sedgwick 2014). As such, the only outcomes that were possible are association related, not causal related. However, we have to still emphasize that a cross-sectional study was a suitable design for the current study to satisfy the overall aim that was to estimate the prevalence and multiple risk factors of cervical precancerous lesions at the same time (Sedgwick 2014).

Even though in the current study it was not possible confirm some other associations with risk factors for the development of cervical precancerous lesions among WLHIV, the notable findings from this study may be used as the basis to develop other hypotheses for more robust studies such as case control and other follow-up cohort studies (Sedgwick, 2014).

Because some of the events being examined in the current study occurred in the past, there was a potential for recall bias. Another potential challenge was getting the women to report some of the risk factors such as the history of sex work and the number of lifetime sexual partners. Reporting on these risk factors could be opening potential stigmatization, hence, it is possible that some study participants were reluctant to share the correct information. However, it is important to note that the researchers of the current study assured the participants that their information and identity would be kept confidential at all times, and the interviews were also conducted at very secure clinic rooms where only the interviewer and the participants were present.

On contraceptive use, the tool which was being used (CCSTPR) only indicated the type as being oral, injectable. In Namibia the types of oral contraception are combined oral contraceptives and POP while for the injectables there are two types available in the public sector as well as implants (MoHSS, 2021). Knowing specific types of contraceptives and duration of use would have allowed for a more detailed assessment of the potential risk factors associated with the specific types of contraceptives. This therefore calls for more similar studies to be done in the near future to unpack this form of information.

The current study did not explore the role of alcohol as a risk factor for the development of precancerous lesions of the cervix, even though there is Namibia evidence that suggests that 65.8% of women are actively consuming alcohol (He, Bishwajit and Yaya, 2019). Moreover, the 2013 DHS showed that in Namibia, 45% of women consumed one to two alcoholic drinks per day (MoHSS and ICFI, 2014). Alcohol has been associated with increased risk of development of cancer of the cervix in some publications as discussed below. In a case-control

study in Italy, women who consumed alcohol regularly were 1.28 times more likely to present with ICC than those who did not consume alcohol 95% CI: (1.04–1.59) (Chiaffarino *et al.*, 2002). Singini *et al*. (2021) found that heavy alcohol consumption was responsible for 5.6% of ICC in their study based in South Africa. It is postulated that heavy alcohol use is associated with risky sexual behaviours such as multiple sexual partners which may predispose to acquisition of high-risk HPV infection (Chiaffarino *et al.*, 2002; Singini *et al.*, 2021). This therefore calls for more similar studies to be done in the near future to unpack this form of information.

5.7 Conclusion

From the literature review above it is magnified that cervical cancer is a significant global public health concern, and more so in LMICs. This is unfortunate as this health condition is preventable as shown by evidence from successful cervical cancer screening and prevention programs in some HICs. In the current study it is also shown that in Namibia and indeed in Katima Mulilo, there is a high incidence of premalignant lesions of the cervix in WLHIV which are harbingers of ICC. It is also shown that there are recognizable risk factors for the development of premalignant lesions like early sexual debut, early marriage and multiple sexual partners. Being on ART was found to be protective from developing precancerous lesions of the cervix. The implications of the above findings will be further elucidated in the recommendations below.

CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

6.1 HPV-vaccination

The WHO cervical cancer elimination strategy aims to have 90% of all girls before the age of 15 years by 2030, however the vaccine and guidelines for HPV vaccination in Namibia are not yet available in the public sector (Korn *et al.*, 2022). The types of vaccines available have the potential to protect against the 70% to 90% of cervical cancers depending on the number of HPV types they cover (Cheng, Wang and Du, 2020). The WHO (2020) current guidelines recommend that girls aged between 9 years and 14 years receive two doses of vaccine to be fully protected and that high vaccine coverage affords protection to unvaccinated individuals through herd immunity.

Only less than 30% of LMICs had gone on to implement national cervical cancer screening programs by May 2020; Namibia included, this was compared to more than 80% of high-income countries (Sung *et al.*, 2021). The advantages of having high vaccination rates can be illustrated by the observation made in Australia which showed a 38% reduction in precancerous lesions in girls after achieving 70% vaccination coverage in both girls and boys below 14 years of age. The high VIA positivity rates observed in the current study and the rates observed by Korn *et al*. (2022) from the Namibia program data make a compelling case for the introduction of a national cervical cancer vaccination program. According to WHO (2020); vaccination should be part of a comprehensive prevention program which incorporates age appropriate sexual and reproductive health information on delaying sexual debut, reducing sexual partners and promoting condom use.

6.2 HPV-DNA testing

The WHO (2021) recommends that DNA-HPV testing be the primary screening test instead of VIA or Pap smear approach in women in the general population and WLHIV. However existing programs using VIA as a primary screening should transition rapidly due to challenges with quality assurance associated with VIA based screening (WHO, 20210). Indeed; the sensitivity of the VIA procedure has been described from 41% to 92%, these variations have been attributed to individual interpretation related to training and experience, variations in the light source and storage and quality of the acetic acid used (Namale *et al.*, 2021).

Human papilloma virus-deoxyribonucleic acid testing has higher specificity and negative predictive value than VIA, meaning that if one receives a negative result the interval to a retest is less than if the screening test was VIA (WHO, 2020). This molecular test (HPV-DNA) testing allows for self-testing as well as health care worker testing, self-testing contributes to increased accessibility and acceptability allowing for greater coverage (WHO, 2020). The ability for self-testing of the HPV-DNA screening makes this method more acceptable and accessible to women in Namibia which is vast and sparsely populated making access to well-equipped adequately staffed health facilities out of reach for some women.

6.3 Empowering adolescent girls and young women

From the cross-sectional study it was noted that having multiple sexual partners, early sexual debut and early marriage were factors associated with the development of precancerous lesions of the cervix. The prevalence of child marriage in Namibia according to the child marriage report of 2020 was at 18.4% for women which is quite high (MGEPESW, UNICEF and UNFPA, 2020). The same report suggests that poverty and lack of educational opportunities

lead to early marriage which exposes the children to an early sexual debut (MGEPESW, UNICEF and UNFPA, 2020). The vulnerabilities mentioned above also put the adolescent girls and young women (AGYW) at a 14 times risk of HIV acquisition compared to their male counterparts further increasing the risks of developing precancerous cervical lesions (USAID, 2022).

Strengthening programs like the Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe (DREAMS) offering package interventions addressing structural factors which make AGYW vulnerable is one way to reduce early marriages, sexual debut and sexual partners (USAID, 2022). The interventions through the DREAMS program are aimed at economic inclusion, increased access to secondary schooling and promoting access to friendly sexual and reproductive services (USAID, 2022). Such programs as the DREAMS program are primarily aimed at HIV negative AGYW, however the same approach can also be replicated to cater for AGYW LWHIV as they also benefit from economic inclusion, improved educational opportunities as access to friendly sexual and reproductive services.

6.4 Improving access for marginalized communities

Results from this cross-sectional study showed that none of the study participants were engaged in sex-work, however from Jonas *et al*. (2020) there are up to 800 FSWs in Katima Mulilo and up to 52% of them are LWHIV while national data suggests that only about 33.7% were on ART. These findings could be an opportunity to study FSWs and assess their access to ART and cervical cancer screening services and sexual and reproductive health services. Due to the nature of their profession FSWs are at an enhanced risk for the development of precancerous lesions and therefore ICC as they are likely to have multiple sexual partners, exposed to STIs especially high-risk HPV (Namale *et al.*, 2021). Our study demonstrated that being on ART

for more than five years is protective to the development of precancerous lesions of the cervix, however the national data indicates that only 33.7% of FSWs are accessing ART (Jonas *et al*., 2020). The MoHSS and other stakeholders may need to do further research into the barriers to ART linkage and retention including ways to engage FSWs into care.

6.5 Further research

It has been elucidated in the current study that there are relationships between the development of precancerous lesions and factors like multiple sexual partners, time of sexual debut, duration on ART, age of marriage and parity. There is still need to explore other potential risk factors like alcohol use, level of income and a more refined study into contraceptive use looking at the specific types of contraceptives being used as well as duration of use.

As this was a cross sectional study causation may be difficult to confirm but association of risk factors with the development of precancerous lesions may be conferred, however the results from this study may be used as a basis for more robust studies like cohort studies (Sedgwick, 2014).

REFERENCES

1. Ali-Risasi, C. *et al.* (2015) 'Prevalence and Risk Factors for Cancer of the Uterine Cervix among Women Living in Kinshasa, the Democratic Republic of the Congo: A cross-sectional study', *Infectious Agents and Cancer*, 10(1). Available at: https://doi.org/10.1186/s13027-015-0015-z.
2. Belayneh, T., Mitiku, H. and Weldegebreal, F. (2019) 'Precancerous Cervical Lesion and Associated Factors among HIV-Infected Women on ART in Amhara Regional State, Ethiopia: A Hospital-Based Cross-Sectional Study', *Int J Health Sci (Qassim)*, 13(3), pp. 4–9.
3. Bray, F. *et al.* (2018) 'Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries', *CA: A Cancer Journal for Clinicians*, 68(6), pp. 394–424. Available at: https://doi.org/10.3322/caac.21492.
4. Brisson, M. *et al.* (2020) 'Impact of HPV Vaccination and Cervical Screening on Cervical Cancer Elimination: A Comparative Modelling Analysis in 78 Low-Income and Lower-Middle-Income Countries', *Lancet (London, England)*, 395(10224), pp. 575–590. Available at: https://doi.org/10.1016/S0140-6736(20)30068-4.
5. Bruce, N., Pope, D. and Stanistreet, D. (2008) *Quantitative Methods for Health Research: A Practical Interactive Guide to Epidemiology and Statistics, Quantitative Methods for Health Research*. Chichester, UK: John Wiley & Sons, Ltd. Available at: https://doi.org/10.1002/9780470725337.REFS.
6. Bruni, L. *et al.* (2021) *Human Papillomavirus and Related Diseases Report NAMIBIA*. Barcelona. Available at: www.hpvcentre.net (Accessed: 30 August 2022).

7. Cheng, L., Wang, Y. and Du, J. (2020) 'Human Papillomavirus Vaccines: An Updated Review', *Vaccines*. MDPI AG, pp. 1–15. Available at: https://doi.org/10.3390/vaccines8030391.
8. Chiaffarino, F. *et al.* (2002) 'Correspondence RE: Weiderpass et al., Alcoholism and Risk of Cancer of Cervix Uteri, Vagina, and Vulva. Cancer Epidemiol. Biomark. Prev., 10: 899–901, 2001', *Cancer Epidemiology, Biomarkers & Prevention*, 11(3), pp. 325–326. Available at: http://aacrjournals.org/cebp/article-pdf/11/3/325/1740830/ce0302000325.pdf.
9. Chichareon, S. *et al.* (1998) *Risk Factors for Cervical Cancer in Thailand: A Case-Control Study*. Available at: https://academic.oup.com/jnci/article/90/1/50/1081418.
10. Chin'ombe, N. *et al.* (2014) *Human Papillomavirus Genotypes in Cervical Cancer and Vaccination Challenges in Zimbabwe*. Available at: http://www.infectagentscancer.com/content/9/1/16.
11. Corral, F. *et al.* (1996) 'Limited Education as a Risk Factor in Cervical Cancer', *Bulletin of the Pan American Health Organization*, 30(4), pp. 322–329.
12. Durowade, K.A. *et al.* (2012) 'Prevalence and Risk Factors of Cervical Cancer among Women in an Urban Community of Kwara State, North Central Nigeria', *Journal of Preventive Medicine and Hygiene*, 53(4), pp. 213–219. Available at: https://doi.org/10.15167/2421-4248/jpmh2012.53.4.351.
13. Francis, S.C. *et al.* (2014) 'Epidemiology of Curable Sexually Transmitted Infections among Women at Increased Risk for HIV in Northwestern Tanzania: Inadequacy of Syndromic Management', *PLOS ONE*, 9(7), p. e101221. Available at: https://doi.org/10.1371/JOURNAL.PONE.0101221.

14. Gabaza, C. *et al.* (2019) 'Utilization and Outcomes of Cervical Cancer Screening Services in Harare City, 2012-2016: A Secondary Data Analysis', *BMC Health Services Research*, 19(1), p. 454. Available at: https://doi.org/10.1186/s12913-019-4314-8.
15. Getinet, M. *et al.* (2015) 'Prevalence and Predictors of Pap Smear Cervical Epithelial Cell Abnormality among HIV-Positive and Negative Women Attending Gynecological Examination in Cervical Cancer Screening Center at Debre Markos Referral Hospital, East Gojjam, Northwest Ethiopia', *BMC Clinical Pathology*, 15(1). Available at: https://doi.org/10.1186/s12907-015-0016-2.
16. Hamoonga, T.E. *et al.* (2017) 'Higher Educational Attainment Associated with Reduced Likelihood of Abnormal Cervical Lesions Among Zambian Women - a Cross Sectional Study', *BMC Cancer*, 17(1), pp. 1–12. Available at: https://doi.org/10.1186/S12885-017-3680-Z/TABLES/5.
17. He, Z., Bishwajit, G. and Yaya, S. (2019) 'Prevalence of Alcohol and Tobacco Use among Men and Women in Namibia', *International Journal of Environmental Research and Public Health*, 16(1). Available at: https://doi.org/10.3390/IJERPH16010059.
18. Health Knowledge (2022) *Validity, Reliability and Generalisability | Health Knowledge*, *https://www.healthknowledge.org.uk/*. Available at: https://www.healthknowledge.org.uk/content/validity-reliability-and-generalisability (Accessed: 7 September 2022).
19. Izudi, J., Adrawa, N. and Amongin, D. (2016) 'Precancerous Cervix in Human Immunodeficiency Virus Infected Women Thirty Years Old and above in Northern Uganda', *Journal of Oncology*, 2016. Available at: https://doi.org/10.1155/2016/5473681.
20. Jolly, P.E. *et al.* (2017) 'Screening, Prevalence, and Risk Factors for Cervical Lesions among HIV Positive and HIV Negative Women in Swaziland', *BMC Public Health*, 17(1). Available at: https://doi.org/10.1186/s12889-017-4120-3.

21. Jonas, A. *et al.* (2020) 'HIV Prevalence, Risk Factors for Infection, and Uptake of Prevention, Testing, and Treatment among Female Sex Workers in Namibia', *Journal of Epidemiology and Global Health*, 10(4), pp. 351–358. Available at: https://doi.org/10.2991/JEGH.K.200603.001.

22. Kassa, L.S. *et al.* (2019) 'Precancerous Lesions of Cervix among Women Infected with HIV in Referral Hospitals of Amhara Region, Northwest Ethiopia: A cross sectional study', *African Health Sciences*, 19(1), pp. 1695–1704. Available at: https://doi.org/10.4314/ahs.v19i1.46.

23. Kelly, H. *et al.* (2018) 'Association of Antiretroviral Therapy with high-risk Human Papillomavirus, Cervical Intraepithelial Neoplasia, and Invasive Cervical Cancer in Women Living with HIV: A Systematic Review and Meta-Analysis', *The Lancet HIV*, 5(1), pp. e45–e58. Available at: https://doi.org/10.1016/S2352-3018(17)30149-2.

24. Korn, A.K. *et al.* (2022) 'Cervical Cancer Screening and Treatment, HIV Infection, and Age: Program Implementation in Seven Regions of Namibia', *PLoS ONE*, 17(2 February). Available at: https://doi.org/10.1371/journal.pone.0263920.

25. Kuguyo, O. *et al.* (2017) 'Cervical Cancer in Zimbabwe: A Situation Analysis', *Pan African Medical Journal*, 27. Available at: https://doi.org/10.11604/PAMJ.2017.27.215.12994.

26. Lem Asangbeh-Kerman, S. *et al.* (2021) 'Cervical Cancer Prevention in Countries with the Highest HIV Prevalence: A Review of Policies'. Available at: https://doi.org/10.1186/s12889-022-13827-0.

27. Lemu, L.G. *et al.* (2021) 'Precancerous Cervical Lesions among HIV-Infected Women Attending HIV Care and Treatment Clinics in Southwest Ethiopia: A Cross-Sectional Study', *International Journal of Women's Health*, 13, pp. 297–303. Available at: https://doi.org/10.2147/IJWH.S295137.

28. Liu, G. *et al.* (2018) 'HIV-positive Women Have Higher Risk of Human Papilloma Virus Infection, Precancerous Lesions, and Cervical Cancer', *AIDS*, 32(6), pp. 795–808. Available at: https://doi.org/10.1097/QAD.0000000000001765.
29. Loopik, D.L. *et al.* (2020) 'Oral Contraceptive and Intrauterine Device Use and The Risk of Cervical Intraepithelial Neoplasia Grade III or Worse: A Population-Based Study', *European Journal of Cancer*, 124, pp. 102–109. Available at: https://doi.org/10.1016/j.ejca.2019.10.009.
30. Louie, K.S. *et al.* (2009) 'Early Age at First Sexual Intercourse and Early Pregnancy are Risk Factors for Cervical Cancer in Developing Countries', *British Journal of Cancer*, 100(7), pp. 1191–1197. Available at: https://doi.org/10.1038/sj.bjc.6604974.
31. Macleod, C.I. and Reynolds, J.H. (2021) 'Human Papilloma Virus Infection and Cervical Cancer among Women who Sell Sex in Eastern and Southern Africa: A Scoping Review', *Women's health (London, England)*, 17. Available at: https://doi.org/10.1177/17455065211058349.
32. Makuza, J.D. *et al.* (2015) 'Prevalence and Risk Factors for Cervical Cancer and Pre-Cancerous Lesions in Rwanda', *Pan African Medical Journal*, 22. Available at: https://doi.org/10.11604/pamj.2015.22.26.7116.
33. MGEPESW, UNICEF and UNFPA (2020) *National Formative Study on Child Marriage Republic of Namibia Ministry of Gender Equality, Poverty Eradication and Social Welfare*. Windhoek.
34. MoHSS (2018) *National Cervical Cancer Prevention Guidelines*. 1st Ed. Windhoek: Ministry of Health and Social Services, Namibia.
35. MoHSS (2019) *Namibia Population-based HIV Impact Assessment 2017 (NAMPHIA)*. Windhoek.

36. MoHSS (2021) *Namibia Standard Treatment Guidelines*. 2nd Ed. Windhoek: Ministry of Health and Social Services, Pharmaceutical Services.
37. MoHSS and ICFI (2014) 'Namibia 2013 Demographic and Health Survey'. Available at: https://dhsprogram.com/pubs/pdf/FR298/FR298.pdf.
38. Moreno, V. *et al.* (2002) 'Effect of Oral Contraceptives on Risk of Cervical Cancer in Women with Human Papillomavirus Infection: the IARC Multicentric Case-Control Study', *The Lancet*, 359(9312), pp. 1085–1092.
39. Namale, G. *et al.* (2021) 'Visual Inspection with Acetic Acid (VIA) Positivity among Female Sex Workers: A Cross-sectional Study Highlighting One-year Experiences in Early Detection of Pre-cancerous and Cancerous Cervical Lesions in Kampala, Uganda', *Infectious Agents and Cancer*, 16(1). Available at: https://doi.org/10.1186/s13027-021-00373-4.
40. Nkfusai, N.C. *et al.* (2019) 'Prevalence of precancerous cervical lesions in women attending Mezam Polyclinic Bamenda, Cameroon', *Pan African Medical Journal*, 32. Available at: https://doi.org/10.11604/pamj.2019.32.174.16895.
41. Obure, J. *et al.* (2009) 'Prevalence and Severity of Cervical Squamous Intraepithelial Lesion in a Tertiary Hospital in Northern Tanzania.', *Tanzania journal of health research*, 11(4), pp. 163–169. Available at: https://doi.org/10.4314/thrb.v11i4.50143.
42. Ono, A. *et al.* (2019) 'Relationship between Tobacco Smoking and Cervical Cancer', *Women's Health – Open Journal*, 5(1), pp. 19–21. Available at: https://doi.org/10.17140/WHOJ-5-133.
43. Palefsky, J. (2009) 'Human Papillomavirus related Disease in People with HIV', *Curr Opin HIV AIDS*, 4(1), pp. 52–56. Available at: https://doi.org/10.1097/COH.0b013e32831a7246
44.

45. Pourhoseingholi, M.A., Vahedi, M. and Rahimzadeh, M. (2013) 'Sample Size Calculation in Medical Studies', *Gastroenterology and Hepatology rom Bed to Bench*, 6(1), p. 14. Available at: /pmc/articles/PMC4017493/ (Accessed: 5 September 2022).
46. Ramogola-Masire, D. *et al.* (2022) 'Support for Lowering Cervical Cancer Screening age to 25 for Women Living with HIV: Retrospective Cross-Sectional Programmatic Data from Botswana', *BMC Women's Health*, 22(1). Available at: https://doi.org/10.1186/s12905-022-01680-7.
47. Roura, E. *et al.* (2016) 'The Influence of Hormonal Factors on the Risk of Developing Cervical Cancer and Pre-Cancer: Results from the EPIC Cohort', *PLoS ONE*, 11(1). Available at: https://doi.org/10.1371/journal.pone.0147029.
48. Sedgwick, P. (2014) 'Cross Sectional Studies: Advantages and Disadvantages', *BMJ (Online)*. BMJ Publishing Group. Available at: https://doi.org/10.1136/bmj.g2276.
49. Singini, M.G. *et al.* (2021) 'Ranking Lifestyle Risk Factors for Cervical Cancer among Black Women: A Case-Control Study from Johannesburg, South Africa', *PLOS ONE*, 16(12), p. e0260319. Available at: https://doi.org/10.1371/JOURNAL.PONE.0260319.
50. Stelzle, D. *et al.* (2021) 'Estimates of the Global Burden of Cervical Cancer Associated with HIV', *The Lancet Global Health*, 9(2), pp. e161–e169. Available at: https://doi.org/10.1016/S2214-109X(20)30459-9.
51. Suehiro, T.T. *et al.* (2021) 'High Molecular Prevalence of HPV and other Sexually Transmitted Infections in a Population of Asymptomatic Women who Work or Study at a Brazilian University', *Revista do Instituto de Medicina Tropical de Sao Paulo*, 63, pp. 1–10. Available at: https://doi.org/10.1590/s1678-9946202163001.
52. Sung, H. *et al.* (2021) 'Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries', *CA: A Cancer Journal for Clinicians*, 71(3), pp. 209–249. Available at: https://doi.org/10.3322/caac.21660.

53. Taye, B.T., Mihret, M.S. and Muche, H.A. (2021) 'Risk Factors of Precancerous Cervical Lesions: The Role of Women's Socio-demographic, Sexual Behavior and Body Mass Index in Amhara Region Referral Hospitals; Case-Control Study', *PLoS ONE*, 16(3 March). Available at: https://doi.org/10.1371/journal.pone.0249218.
54. Tsehay, B. and Afework, M. (2020) 'Precancerous Lesions of the Cervix and its Determinants among Ethiopian Women: Systematic Review and Meta-analysis', *PLoS ONE*, 5(10), e0240353. Available at: https://doi.org/10.1371/journal.pone.0240353.
55. USAID (2022) *DREAMS: Partnership to Reduce HIV/AIDS In Adolescent Girls and Young Women | U.S. Agency for International Development*, *United States Agency for International Development*. Available at: https://www.usaid.gov/global-health/health-areas/hiv-and-aids/technical-areas/dreams (Accessed: 6 September 2022).
56. Weldegebreal, F. and Worku, T. (2019) 'Precancerous Cervical Lesion Among HIV-Positive Women in Sub-Saharan Africa: A Systematic Review and Meta-Analysis', *Cancer Control*, 26(1), pp. 1–11. Available at: https://doi.org/10.1177/1073274819845872.
57. Wesson, P.D. *et al.* (2019) 'Estimating the Population Size of Female Sex Workers in Namibia Using a Respondent-Driven Sampling Adjustment to the Reverse Tracking Method: A Novel Approach', *JMIR public health and surveillance*, 5(1). Available at: https://doi.org/10.2196/11737.
58. WHO (2017) *Trainees' Handbook Cervical Cancer Screening and Management of Cervical Pre-Cancers*. New Delhi: World Health Organization, Regional Office for South East Asia.
59. WHO (2020) *Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem*. Geneva: World Health Organization. Available at: http://apps.who.int/bookorders.

60. WHO (2021) *WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition*. Second. Geneva: World Health Organization. Available at: http://apps.who.int/bookorders.
61. WHO (2022) *Noncommunicable Disease Progress Monitor 2022*. Geneva.
62. Woromogo, S.H. *et al.* (2021) 'Uterine Cervical Neoplasms Mass Screening at the University Hospital Centre of Libreville, Gabon: Associated Factors with Precancerous and Cancerous Lesions', *PLoS ONE*, 16(7 July). Available at: https://doi.org/10.1371/journal.pone.0255289.
63. Zhang, X. *et al.* (2021) 'Trends of Cervical Cancer at Global, Regional, and National Level: Data from the Global Burden of Disease Study 2019', *BMC Public Health*, 21(1). Available at: https://doi.org/10.1186/s12889-021-10907-5.

APPENDICES

Appendix 1. Structured Questionnaire

STRUCTURED QUESTIONNAIRE: English				
Patient ID Number:				
Date of Birth:				
Age:				
	Single	Married	Divorced	
Marital status:				
	Never attended school	Primary school	Secondary school	College/ University
Highest level of education				
How do you earn your income?				
Have you ever exchanged sexual favours for any kind of payment?				
	Yes		No	
Are you using any form of contraception				

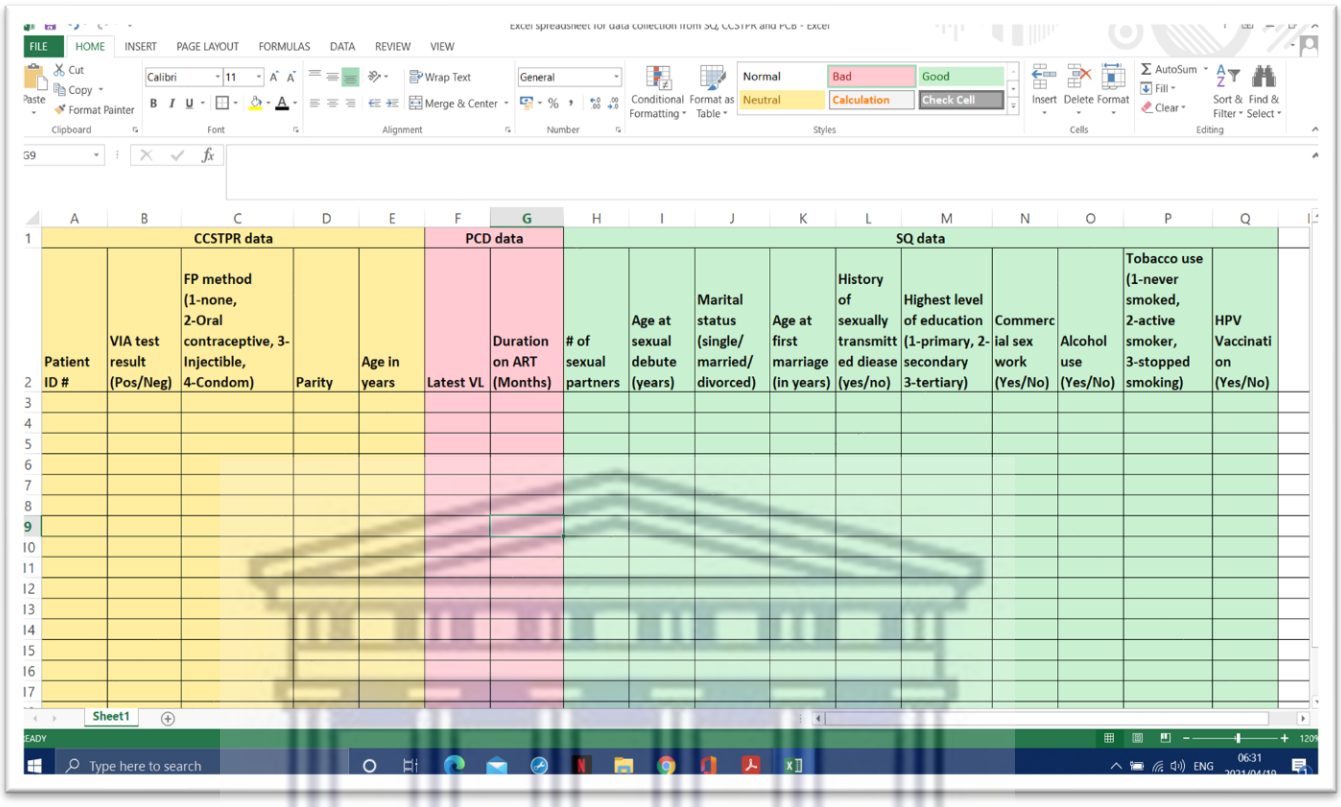
	Oral contraceptive	Injectable contraceptive	IUCD	Condoms
If yes what kind?				
How long have you been on the current contraceptive method?				
	Yes		No	
Do you drink alcohol?				
	Yes		No	
Do you use tobacco?				
If yes how many cigarettes per day?				
How old were you when you were first married?				
How many sexual partners have you had in your life?				
At what age did you start having sexual intercourse?				
	Yes		No	
Have you ever been treated with a sexually transmitted infection?				
If yes, do you know which one?				
	Yes		No	
Have you ever been immunised against Human Papilloma Virus (HPV)				

STRUCTURED QUESTIONNAIRE: Silozi				
Nombole ya buizibahoza ya mukuli				
Silimo sa kupepwa:				
Lilimo za kupepwa:				
	Ha mu sika nyalwa	Munyezwi	Mukauhani	
Maemo a linyalo:				
	Ha mu sika kena sikolo	Litopa za makalelo	Litopa ze pahami	Sikolo sa maemo a pahami
Mukeni sikolo kuyoli mwa sitopa mańi?				
Mufumana masheleni mwa nzila ye cwańi?				
Se mukile mwa itenga mwa litaba za kusomana kuli mufumane tuwelo?				
	Eni		Awa	
Muna ni nzila ye musebelisa ku sileleza kuitwala				

	Pilusi ya silelezo	Ndonga	IUCD	Kondomu
Haiba kicwalo ki mukwa ufi?				
Ki nako ye kuma kai ye se muinzi kuona muhato wa silelezo wo?				
	Eni		Awa	
Mwa nwa bucwala?				
	Eni		Awa	
Mwa zuba kwai?				
Haiba kuli eni, ki misanga ye mi kai ka zazi?				
Ne munyezwi la pili inge muna ni lilimo ze kai?				
Muse mubile ni balikani ba kusomana ni bona ba ba kai mwa bupilo bwa mina?				
Mukalile kuitenga mwa kusomana inge muna ni lilimo ze kai?				
	Eni		Awa	
Ne se mu kile mwa alafiwa butuku bwa siozwa?				
Haiba ki cwalo ki butuku mańi?				
	Eni		Awa	

Kana ne se mufumani mupendo wa silelezo kwa kokwani ya Human Papilloma Virus? **(kokwani ye ifumanwa ka kusomana ni ku ngunyutana ni mutu yana ni yona)**		

Appendix 2. Excel Spreadsheet for Data Collection from the SQ, CCSTPR and PCB



	CCSTPR data					PCD data		SQ data									
	Patient ID #	VIA test result (Pos/Neg)	FP method (1-none, 2-Oral contraceptive, 3-Injectible, 4-Condom)	Parity	Age in years	Latest VL	Duration on ART (Months)	# of sexual partners	Age at sexual debute (years)	Marital status (single/ married/ divorced)	Age at first marriage (in years)	History of sexually transmitted diease (yes/no)	Highest level of education (1-primary, 2-secondary 3-tertiary)	Commercial sex work (Yes/No)	Alcohol use (Yes/No)	Tobacco use (1-never smoked, 2-active smoker, 3-stopped smoking)	HPV Vaccination (Yes/No)
3																	
4																	
5																	
6																	
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17																	

Appendix 3. University of the Western Cape's Biomedical Research Ethics Committee Approval

UNIVERSITY of the WESTERN CAPE

60 YEARS of hope, action & knowledge

10 June 2021

Dr S Mpariwa
School of Public Health
Faculty of Community Health Sciences

Ethics Reference Number: BM21/4/3

Project Title: Prevalence of and risk factors for cervical pre-cancerous lesions in HIV positive 20-49-year-old women in the Zambezi region of Namibia.

Approval Period: 08 June 2021 – 08 June 2024

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above mentioned research project.

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

Please remember to submit a progress report annually by 30 November for the duration of the project.

Permission to conduct the study must be submitted to BMREC for record-keeping.

The Committee must be informed of any serious adverse event and/or termination of the study.

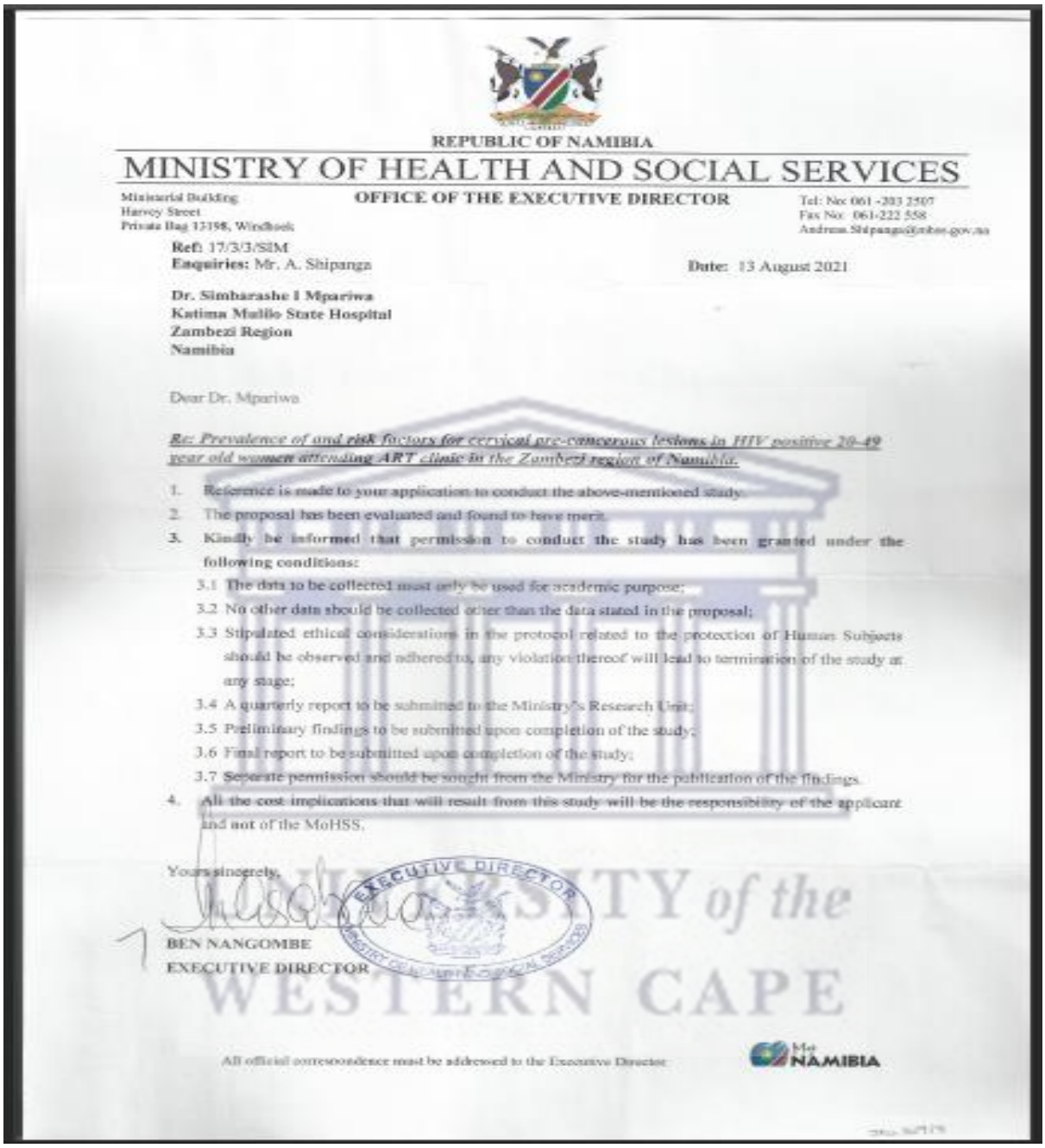
Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

Director: Research Development
University of the Western Cape
Private Bag X 17
Bellville 7535
Republic of South Africa
Tel: +27 21 959 4111
Email: research-ethics@uwc.ac.za

NHREC Registration Number: BMREC-130416-050

FROM HOPE TO ACTION THROUGH KNOWLEDGE.

Appendix 4. Namibian Biomedical Research Ethics Committee (BREC) and Research Management Committee Approval



REPUBLIC OF NAMIBIA

MINISTRY OF HEALTH AND SOCIAL SERVICES

Ministerial Building
Harvey Street
Private Bag 13198, Windhoek

OFFICE OF THE EXECUTIVE DIRECTOR

Tel: No: 061 -203 2507
Fax No: 061-222 558
Address.Shipanga@mhss.gov.na

Ref: 17/3/3/SIM
Enquiries: Mr. A. Shipanga

Date: 13 August 2021

Dr. Simbarashe I Mpariwa
Katima Mulilo State Hospital
Zambezi Region
Namibia

Dear Dr. Mpariwa

Re: Prevalence of and risk factors for cervical pre-cancerous lesions in HIV positive 20-49 year old women attending ART clinic in the Zambezi region of Namibia.

1. Reference is made to your application to conduct the above-mentioned study.
2. The proposal has been evaluated and found to have merit.
3. Kindly be informed that permission to conduct the study has been granted under the following conditions:
   3.1 The data to be collected must only be used for academic purpose;
   3.2 No other data should be collected other than the data stated in the proposal;
   3.3 Stipulated ethical considerations in the protocol related to the protection of Human Subjects should be observed and adhered to, any violation thereof will lead to termination of the study at any stage;
   3.4 A quarterly report to be submitted to the Ministry's Research Unit;
   3.5 Preliminary findings to be submitted upon completion of the study;
   3.6 Final report to be submitted upon completion of the study;
   3.7 Separate permission should be sought from the Ministry for the publication of the findings.
4. All the cost implications that will result from this study will be the responsibility of the applicant and not of the MoHSS.

Yours sincerely,

EXECUTIVE DIRECTOR
MINISTRY OF HEALTH AND SOCIAL SERVICES

BEN NANGOMBE
EXECUTIVE DIRECTOR

All official correspondence must be addressed to the Executive Director

Moi NAMIBIA

Appendix 5. Application to the Namibian Biomedical Research Ethics Committee (BREC) and Research Management Committee

FACULTY OF COMMUNITY AND HEALTH SCIENCES
School of Public Health

Private Bag X17, Bellville, 7535
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Tel: +27 (0) 21 959 9382
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DATE

Office of the Executive Director
Ministry of Health and Social Services
Division: Research
Ministerial Building
Harvey street Windhoek

Re: Prevalence of and risk factors for cervical pre-cancerous lesions in HIV positive 20-49year old women attending ART clinic in the Zambezi region of Namibia

Dear Sir/Madam
I am kindly applying for authorization to conduct an observational study for my mini thesis for the purposes of completing my master's in public health with the University of Western Cape.

This study is a cross sectional study aimed at determining the prevalence of pre-cancerous cervical lesions detected during visualisation of the cervix under acetic acid (VIA) screening and risk factors associated with the development of such lesions in HIV positive women attending Katima Mulilo ART clinic in Namibia. The study will include approximately 330 women between 20-49 years who are being screened for cervical cancer form April 2021 to July 2021. The details of the study can also be viewed in the attached proposal. This study have been approved by the University of the Western Cape's Ethics Committee. Ref No: BM21/4/3. The ethics approval letter is also attached.

A WHO Collaborating Centre for Research and Training in Human Resources for Health

UNIVERSITY of the WESTERN CAPE

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Mobile: +27 824940682
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Email:dcooper@uwc.ac.za
Website: www.uwc.ac.za/publichealth

The outcomes of the committee will be shared with the Ministry of Health and Social Services (MoHSS) management and a copy of the report will also be sent to you for your information. Please do not hesitate to contact me on 3908598@myuwc.ac.za or telephone +264814775551 with any questions that may arise from this application.

Thank you for your continued support of our research.

Sincerely,

Simbarashe Mpariwa
Principal Investigator

Attachments

1. Mini-thesis proposal
2. Ethics Approval from University of Western Cape
3. Consent forms
4. Information sheet
5. Standardised Questionnaire

A WHO Collaborating Centre for Research and Training in Human Resources for Health

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