UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

THE EPIDEMIOLOGY AND KNOWLEDGE OF CERVICAL CANCER IN ZIMBABWE

by

Witness Mapanga
(15252061)

Supervisor: Dr Elvira Singh

Co-supervisors: Prof Brendan Girdler-Brown
Prof Tsungai Chipato

Department: Epidemiology and Biostatistics

SUBMITTED IN FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE

Philosophiae Doctor in Epidemiology

in the School of Health Systems & Public Health
Faculty of Health Sciences

University of Pretoria

Pretoria

2018

DECLARATION

I declare that the thesis, which I hereby submit for the degree Philosophiae Doctor in Epidemiology at the University of Pretoria, is my own work and has not previously been submitted by me for a degree at this or any other tertiary institution.

Signed: _____ Date: _____

SUMMARY

Background: Chronic and persistent infection with human papillomavirus (HPV) is the most important factor associated with the development of cervical cancer. Cervical cancer deaths have been on the rise in recent years with 85% of about 270 000 annual deaths occurring in developing countries. The rise in cervical cancer trends in the past two decades has coincided with the human immunodeficiency virus (HIV) epidemic especially in the sub-Saharan African region. With the advent of HIV especially among young people in most of these developing countries, the incidence, morbidity and burden of cervical cancer are likely to continue increasing.

Although cervical cancer prevention/screening and treatment is available in most developing countries, challenges and constraints still exist when it comes to HIV-positive women. Most developing countries, Zimbabwe included, do not have adequate infrastructure, funds, human resources, proper guidelines, and policies, which facilitate the adoption of effective prevention and treatment methods for cervical cancer among HIV-positive women. Therefore, the first part of this study involved two systematic reviews to weigh current evidence on screening and treatment of cervical cancer in HIV-seropositive women. In addition to the burden in HIV-positive women, the rise in HIV-incidence and risky sexual behaviour (multiple sexual partners, early sexual debut and use of contraceptives) among young people (15 to 24 years old), pose as barriers to successful establishment and implementation of cervical cancer control initiatives.

In Zimbabwe, there is underutilisation of available cervical cancer services (although some are expensive) due to lack of knowledge and information about cervical cancer, a patriarchal and conservative society that views cervical cancer as a women's issue. Adding to these issues, Zimbabwe does not have a cancer communication strategy that focuses on cancer risks factors as a cancer primary prevention. The National Cancer Prevention and Control Strategy for

Zimbabwe (2014-2018) highlighted that underfunding has resulted in health education on cervical cancer to be unstructured. Therefore, as Zimbabwe sets out to strengthen cervical cancer prevention with the launch of the National Mass HPV Vaccination drive in May 2018, a number of questions still exists; how can a culturally patriarchal society aid and accept vaccination freely? How can young boys, men and the rest of the community be integrated within cervical cancer prevention programmes? Are there opportunities for HIV-positive women in these initiatives? How can the issue of health inequity which is associated with cervical cancer incidence be addressed?

Aim: This PhD study weighed current evidence on screening and treatment of cervical cancer in HIV-seropositive women in developing countries through two systematic reviews; and assessed the knowledge, attitude and practices of young people towards cervical cancer, prevention/screening, HPV and vaccination.

Methods: The research design was an integrative approach, which utilised a combination of two systematic reviews and a cross-sectional survey. The two systematic reviews explored cervical cancer prevention and treatment modalities for HIV-positive women, whilst the cross-sectional survey assessed young people's knowledge, attitude and practices concerning cervical cancer. Study participants for the cross-sectional survey were recruited through a three-stage cluster design from high schools and universities in Zimbabwe. Knowledge, attitudes and practices were assessed using questions based and adapted from the concepts of the Health Belief Model (HBM) and the Cervical Cancer Measuring tool kit-United Kingdom (UK).

Results: The study found that HPV Deoxyribonucleic acid/Messenger RNA (DNA/mRNA) testing (n=16, 64.0%), visual inspection with acetic acid (VIA) (n=13, 52.0%) and Pap smear (n=11, 44.0%) are the mostly used cervical cancer screening methods. HPV testing has a better

accuracy/efficiency than other methods with a sensitivity of between 80.0-97.0% and specificity of 51.0-78.0%. In addition, the study found that sequential screening using VIA or visual inspection with Lugol's iodine (VILI) and HPV testing has shown better clinical performance in screening HIV-seropositive women. Whilst radiation, chemotherapy, chemoradiation, and surgery have shown the possibility of effectiveness among HIV-seropositive women, cervical cancer stage, immunosuppressive level, and multisystem toxicities due to treatment are associated with treatment completion, prognosis and survival outcomes. Those infected with HIV are of a younger age and have more advanced cervical cancer as compared to those who are HIV-negative. The majority of young people, 87.47% (656/750), claimed to know what cervical cancer is. However, only 43.14% (324/751) had ever heard of cervical cancer prevention/screening and 53% (398/751) did not know about HPV-how it is transmitted or prevented. Misconceptions regarding cervical cancer causes exist, with some young people attributing cervical cancer to use of detergents, certain foodstuffs and having sex with an uncircumcised man.

Conclusion and Recommendations: This research not only reports on the current screening and treatment modalities for cervical cancer among HIV-positive women, but it also offers a lens through which government can generate behavioural changes around cervical cancer among young people. Although cervical cancer screening exists in almost all developing countries, what is missing is both opportunistic and systematic organized population-based screening. Cervical cancer screening programmes need to be integrated into already existing HIV services, to enable early detection and treatment. The study suggests a need to offer opportunistic and coordinated screening programmes that are provider-initiated to young women (from 15 years), especially those who are HIV-infected, to promote early identification of cervical precancerous lesions. Opportunities to include young boys and HIV-positive middle-aged women in the recently launched mass HPV vaccination programmes exist and can

be utilised. Ring-fencing budgets or introducing cancer levies and investing resources in evidence-based screen and treat strategies for precancerous lesions in HIV-seropositive women and young people will reduce morbidity and mortality due to cervical cancer. Developing a standard cervical cancer primary prevention tool that can be integrated into schools can be a step towards addressing health inequity. Research on cervical cancer management of HIV-seropositive patients focusing on the quality of life of those treated, the effectiveness of the treatment method taking into account CD4+ count and ART is required.

Key words

Cervical cancer; HIV; Prevention; Treatment; Developing countries; Zimbabwe; Young people

DEDICATED WITH LOVE, AFFECTION AND GRATITUDE TO

My wife Rutendo Chinomona-Mapanga

&

My research supervisors Dr Elvira Singh, Professor Brendan Girdler-Brown and Professor Tsungai Chipato

ACKNOWLEDGEMENTS

I am eternally grateful to God Almighty for the opportunity to undertake a PhD degree and for all His love and grace upon my life. The PhD journey was exciting and this thesis is a testimony of hard work and perfect working relationships will all my supervisors, Dr Elvira Singh, Professor Brendan Girdler-Brown and Professor Tsungai Chipato, whom I am greatly indebted to. You offered unreserved guidance, nurtured my development as an Epidemiologist and held my hands to make sure I do not stumble along the way. You made the journey an exciting and memorable one and I will forever be indebted to all of you.

I want to thank many people who contributed to this work and the enthusiasm they exhibited. The wonderful early guidance of the work from Professor Shingairai Feresu, we would not have achieved this without you. The fieldwork team of Tatenda Mudehwe and Caroline Chiumburu, who worked tirelessly and diligently to make this a success and a dream come true. To my fellow co-author, Ahmed Elhakeem, your input opened doors for me to indulge in the systematic review world and I thank you for your leadership.

The warmth, encouragement and love from my beautiful wife, Rutendo, spurred me to work even when I felt drained. Her presence made it easy to put together this thesis and I am greatly privileged to have you as my life partner and always being there.

Lastly, I want to thank the School of Health Systems and Public Health and the Association of African Universities (AAU) for funding the fieldwork and data collection of the cross-sectional component of this study.

Witness Mapanga

PUBLICATIONS BASED ON THIS THESIS

International Journal Publications

1. **Mapanga W.** Girdler-Brown B. Feresu S.A. Chipato T. Singh E. (2018) Prevention of Cervical Cancer in HIV-seropositive Women from Developing Countries through cervical cancer screening: A Systematic Review. Syst Rev 2018 7:198. BioMed Central
2. **Mapanga W.** Feresu S.A. Chipato T (2018) **Treatment of cervical cancer in HIV-seropositive women from developing countries: a systematic review protocol.** Syst Rev 2018, 6:91. BioMed Central
3. **Mapanga W.** Feresu S.A. Chipato T (2017) **A commentary on a systematic review protocol and commentary on cervical cancer prevention in HIV-seropositive women from developing countries.** J Comm Pub Health Nurs 2017, 3:3
4. **Mapanga W.** Elhakeem A. Feresu S.A. Maseko F. Chipato T (2017) **Prevention of cervical cancer in HIV-seropositive women from developing countries: a systematic review protocol.** Syst Rev 2017, 6:91. BioMed Central

To be submitted to BMC Systematic Reviews Journal and BMC Cancer Journal for peer review and potential publication by end of November 2018

5. **Mapanga W**. Singh E. Girdler-Brown B. Feresu S.A. Chipato T (2018) **Treatment of cervical cancer in HIV-seropositive women from developing countries: a systematic review**
6. **Mapanga W**. Singh E. Girdler-Brown B. (2018) **Knowledge, attitudes and practices of young people in Zimbabwe on cervical cancer and HPV, current screening methods and vaccination**

Forth-coming publications

7. Mapanga W. Singh E. Girdler-Brown B. (2018) **Improving the legislative system to enhance cervical cancer management in Zimbabwe: time for an inclusive policy?**

8. Mapanga W. Girdler-Brown B. Singh E. (2018) **Inclusion of young-boys and middle-aged HIV-positive women in HPV vaccination: opportunities and health systems challenges**
9. Mapanga W. Girdler-Brown B. Singh E. (2018) **Diagnostic accuracy of cervical cancer screening methods among HIV-seropositive women in developing countries: a meta-analysis**

International Conference Presentations

1. **Mapanga W**, Singh E and Girdler-Brown B. **Knowledge, attitudes and practices of young people in Zimbabwe on cervical cancer and HPV.** 14th Annual Conference of the Public Health Association of South Africa, 10th - 12th September 2018: Khaya iBhubesi, Parys, South Africa
2. **Mapanga W**, Singh E and Girdler-Brown B. **Inclusion of young-boys and middle-aged HIV-positive women in HPV vaccination: opportunities and health systems challenges.** 14th Annual Conference of the Public Health Association of South Africa, 10th - 12th September 2018: Khaya iBhubesi, Parys, South Africa
3. **Mapanga W**, Singh E and Girdler-Brown B. **Improving the legislative system to enhance cervical cancer in Zimbabwe: time for an inclusive policy?** 14th Annual Conference of the Public Health Association of South Africa, 10th - 12th September 2018: Khaya iBhubesi, Parys, South Africa
4. **Mapanga W** and Feresu S. **Prevention and treatment of cervical cancer in HIV-seropositive women from low resource countries: a systematic review.** 12th Annual Conference of the Public Health Association of South Africa, 19 - 22 September 2016: ICC East London, South Africa

Research Symposium Presentations

1. **Mapanga W.** Singh E. Girdler-Brown B (2018) **Knowledge, attitude and practices of young people in Zimbabwe on cervical cancer and HPV, current screening methods and vaccination.** University of the Witwatersrand, Faculty of Health Sciences Research Day & Postgraduate Expo. 6 September 2018
2. **Mapanga W.** Singh E. Girdler-Brown B. **Knowledge, attitude and practices of young people in Zimbabwe on cervical cancer and HPV, current screening methods and vaccination.** University of Pretoria, Faculty of Health Sciences Research Day. 22 August 2018
3. **Mapanga W** and Feresu S (2015) **Prevention and treatment of cervical cancer in HIV-seropositive women from low resource countries: a systematic review.** Faculty Research Day, University of Pretoria, School of Health Systems and Public Health.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

APPENDICES

LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
ARVs	Antiretroviral drugs
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CIN2+	Cervical intraepithelial neoplasia grade 2+
DC	Digital cervicography
EMBASE	Excerpta Medica Database
GAVI	Global Alliance on Vaccines and Immunisations
HAART	Highly active antiretroviral treatment
HBM	Health Belief Model
HC2	Hybrid Capture-2
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
HPV DNA/mRNA	Human papillomavirus Deoxyribonucleic acid/Messenger RNA
HSIL	High-Grade Squamous Intraepithelial Lesion
LEEP	Loop Electrosurgical Excision Procedure
LSIL	Low-Grade Squamous Intraepithelial Lesion
MDGs	Millennium Development Goals
MOHCC	Ministry of Health and Child Care
NAC	National Aids Council
NGOs	Non-Governmental Organisations
OI	Opportunistic Infections clinics
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
RCT	Randomised controlled trial
SAfAIDS	Southern Africa HIV and AIDS Information Dissemination Service
STIs	Sexually Transmitted Infections

SSA	Sub-Saharan Africa
TB	Tuberculosis
UN	United Nations
UNICEF	United Nations Children's Education Fund
UNFPA	United Nations Population Fund
VIA	Visual inspection with acetic acid
VILI	Visual inspection with Lugol's iodine
WHO	World Health Organisation

"If, as is sometimes supposed, science consisted in nothing but the laborious accumulation of facts, it would soon come to a standstill, crushed, as it were, under its own weight…. Two processes are thus at work side by side, the reception of new material and the digestion and assimilation of the old…The work which deserves, but I am afraid does not always receive, the most credit is that in which discovery and explanation go hand in hand, in which not only are new facts presented, but their relation to old ones is pointed out."

Rayleigh 1885

CHAPTER ONE: INTRODUCTION

1.1 Introduction

This thesis, through two systematic reviews, weighs the current evidence to offer an overview of the cervical cancer screening and treatment methods that are being used for HIV-seropositive women in developing countries. Incidence, morbidity and mortality due to cervical cancer continue to rise in developing countries with high HIV prevalence such as Zimbabwe and HIV-seropositive women are at high risk of developing cervical cancer[1,2]. In an era where cervical cancer is now classified as an AIDS-defining disease[3,4], there is need to provide information on what is being done in terms of preventing and treating cervical cancer in HIV-seropositive women in developing countries. Therefore, synthesised evidence may offer policy makers, health systems stakeholders, epidemiologists and researchers the platform to formulate policies, strategies and interventions that might improve the screening and treatment of cervical cancer in HIV-seropositive women. In addition, synthesised evidence on cervical cancer prevention and treatment will strengthen knowledge of research needs of developing countries' and build the capacity, and confidence of clinicians and decision-makers to interrogate and use evidence.

In order to offer concrete structures to screen, identify cervical cancer cases, and reduce the disease burden, there might need to come up with prevention strategies that eliminate and address cervical cancer risk factors in high-risk groups. Most women with cervical cancer, including those who are HIV-positive, present late at the hospitals because of lack of awareness and knowledge of the disease[1]. In Zimbabwe, there is no government communication strategy towards cervical cancer primary prevention and this has created a scenario where the majority of young literate people do not appreciate the severity of cervical cancer[1]. Young people (15 to 24 years old) have become a concerning group because the evidence is showing that they

are linked with many of the risk factors associated with cervical cancer[5]. Therefore, the second part of this thesis will evaluate the knowledge, attitude and practices of young people towards cervical cancer risk factors, prevention/screening, HPV vaccination and treatment. Two theoretical frameworks, namely, the Health Belief Model (HBM) and the Social Ecological Model (SEM), which both believe that individual health behaviour, knowledge and health-seeking perceptions are influenced by the environment and sociodemographic characteristics[6,7], guided the designing of the research, its methodology including data collection instruments and data collection process, recommendations and discussion.

1.2 Contextual Background

Globally, cervical cancer has become the second most common cancer affecting women with about half a million cases and almost 280 000 deaths annually[8,9]. Significantly, 85% of these annual deaths occur in the developing world[9]. Evidence has shown that in SSA, cervical cancer trends are on the rise in the past decades because of lifestyle factors, HIV, STIs and other reproductive issues and this has created a potential public health risk amongst women[10,11].

Progress in the prevention and treatment of cervical cancer has been made but challenges still exist in developing countries. Developing countries are still faced with challenges of financial resources, poor and/or non-existent health infrastructure (laboratories, cervical cancer screening centres), lack of technology and few qualified health personnel aggravated by brain drain[12,13]. These challenges coupled with lack of proper epidemiological data, lack of knowledge, and inadequate information on cervical cancer have created a major public health issue that is threatening to derail the progress made under the millennium development goal (MDG) number five; reducing maternal mortality and achieving universal access to reproductive health. In developing countries, cervical cancer incidence continues to be strongly associated with health inequity, disability in women and premature deaths[14].

In Zimbabwe as with other parts of Central SSA, cervical cancer has become the most common cancer among women as well as the commonest cause of cancer deaths[15]. In 2008, the World Cancer Research Fund International put Zimbabwe among the top 20 countries with the highest incidence of cervical cancer[1]. In 2010, cervical cancer contributed over 32% of all cancer cases in Zimbabwe and 15% of all cancer deaths[1]. This increase in cervical cancer morbidity and mortality has been attributed to high HIV prevalence in Zimbabwe, which has continued to be relatively stable at 14% among adults in the past decade[16].

In Zimbabwe, health education about cervical cancer, HPV, screening and vaccination is poor, underfunded, and only concentrated in the urban settings. This continues to contribute to health inequity[17]. With cervical cancer screening being offered to women who are 21 years and above, almost all cervical cancer initiatives in Zimbabwe prior to May 2018, did not include young people. This scenario may have likely resulted in cervical cancer knowledge to be limited among young people and worse among men who view cervical cancer as a women's issue. To address the objectives of the post-2015 MDGs, the 2030 Agenda for Sustainable Development, it is vital that future cervical cancer initiatives target both women and men since men are part of the cervical cancer web. This warrants an investigation into the knowledge, attitudes and beliefs of young people in Zimbabwe towards cervical cancer, HPV, other risk factors for cervical cancer, cervical cancer screening and HPV vaccination.

As Zimbabwe is among the top 20 countries with the highest cervical cancer incidence in the world[1], quantifiable epidemiological data pertaining to cervical cancer risk factors and potential high-risk groups need to be described, to set up a platform for cervical cancer stakeholders and policymakers to operate from. A number of questions still exist; how much has the HIV epidemic shaped the prevention and treatment methods of cervical cancer, if any? How much do potential risk groups (15 to 24 years) know about cervical cancer, its risk factors, prevention and treatment? These questions require to be answered for a developing country to

facilitate proper structuring of cervical cancer screening, treatment and management in light of limited resources, economic challenges and a conservative socio-cultural environment. In addition, no studies have evaluated the knowledge, attitudes and practices of young people (15 to 24 years) towards cervical cancer, screening and HPV; therefore, this proposed study might contribute some important information to the body of knowledge.

1.3 Study justification

Faced with such a major public health issue that continues to increase both in incidence, morbidity, mortality and exerting pressure on an already struggling health delivery system; the need to investigate the knowledge young people in Zimbabwe have about cervical cancer, screening and HPV vaccination is vital. There is scanty, if any, evidence about young people's knowledge, attitude and practices towards cervical cancer, its causes, screening and HPV vaccination in the developing world. Evidence from Zimbabwe suggests that the incorporation of cervical cancer vaccination and implementation requires a lot of knowledge and understanding on part of young people[17]. This study aimed to provide the government and local partners with relevant information on how to attract young people in addressing risk factors associated with cervical cancer. This would help in the formulation and design of appropriate cervical cancer primary prevention strategies among young people, HIV-positive women and the population at large.

Furthermore, since cervical cancer in young women is being associated more and more with HIV and AIDS in Zimbabwe[1], combined efforts to address these reproductive health challenges need to be streamlined with an understanding that borders on how people view risks associated with cervical cancer and its causes. With this perspective in mind, the inclusion of boys and men in such initiatives will further strengthen the public health initiatives in trying to address the challenges of cervical cancer and its causes.

With vaccination, there is a higher chance of reducing inequalities associated with the burden of cervical cancer in Zimbabwe and success of the HPV vaccination will depend on whether those at higher risk of HPV infection (young people) understand and embrace vaccination to achieve wider vaccination coverage. Having a clear picture of the knowledge, attitude and perceptions of young people, may guide the government and public health specialists in the right direction in rolling out HPV vaccination. Also, this study will give public health practitioners, epidemiologists and clinicians better understanding of the current socio-demographic inequalities in the burden of cervical cancer and help them identify the most at-risk subpopulation that needs cervical cancer services.

The study results may indicate if it is necessary to tailor cervical cancer prevention and treatment interventions to specific needs of the Zimbabwean women based on the identified risk factors. In addition, in the post-2015, it is important that new developmental agendas highlight how a serious public health issue like cervical cancer is to be tackled and addressed in developing countries. This will promote mobilisation and or ring-fencing of resources towards the scaling up of cervical cancer screening and treatment in countries like Zimbabwe.

The information on the screening and treatment of cervical cancer in HIV-seropositive women may further add to the growing calls for developing countries to integrate cervical cancer services into already existing HIV programmes. This ‘one-stop’ service approach has the potential of increasing cervical cancer screening rates among HIV-positive women. This will have a long-term benefit of reducing the number of HIV-positive women that develop cervical cancer. Such knowledge might lead to the development or recommendation of a standardised diagnostic tool for cervical cancer screening among HIV-infected women in developing countries like Zimbabwe.

1.4 Research questions

The research aims to answer the following questions:

- What are the prevention and treatment modalities that are being used to prevent and treat cervical cancer in HIV-seropositive women? Are these the same prevention and treatment modalities that are being used for HIV-negative women? Are the prevention and treatment modalities effective in HIV-seropositive women?
- What are the knowledge, attitude and beliefs among young people with regard to cervical cancer?

  Our overall hypothesis is that by having information pertaining to the knowledge, attitudes and practices of the young people (a potential high-risk group) and synthesised evidence on prevention and treatment of cervical cancer among HIV-seropositive women (a high risk group), this will assist Zimbabwe and the Southern African region in developing context-specific screening and treatment modalities in line with available resources and expertise.

1.5 Research aim

The purpose of this study was to weigh and evaluate published evidence relating to the available cervical cancer screening and treatment modalities for HIV-seropositive women in developing countries through two systematic reviews; and investigate the knowledge, attitudes and beliefs of young people (15 to 24 years old) in Zimbabwe about cervical cancer, its risk factors, cervical cancer screening and HPV vaccination.

1.5.1 Specific Objectives

1. To determine the proportion and describe the socio-demographic characteristics of young people who have ‘enough’ knowledge of cervical cancer causes and its prevention in Zimbabwe.

We hypothesise that the proportion of young people with enough knowledge of cervical cancer is low and those with knowledge would have been associated with cervical cancer either directly or indirectly

2. To determine if young people have enough knowledge about HPV, how it is transmitted and prevented.

   Young people's knowledge of HPV, how it is transmitted and prevented is not known. However, we hypothesise that their knowledge is low.

3. To assess young people's overall knowledge of cervical cancer, available preventative measures and treatment options in Zimbabwe.

   We hypothesise that the overall knowledge of cervical cancer, preventative measures and treatment among the young people is limited.

4. To determine the reasons for young people's lack of knowledge of cervical cancer causes and their prevention.

   We hypothesise that young people's lack of knowledge of cervical cancer is due to a variety of reasons.

5. To assess the attitude and beliefs of young people towards causes of cervical cancer, screening, HPV and vaccination.

   We hypothesise there are probably incorrect beliefs and attitudes by young people towards causes of cervical cancer, screening, HPV and vaccination.

6. To determine the public health impact of young people's knowledge of the causes of cervical cancer and the available preventative and treatment measures on the health care system.

   We hypothesise that a lack of knowledge of young people's part will have a negative impact on cervical cancer management.

1.6 Chapter One Summary

1.6.1 Research study's overall impact on public health

The impact of cervical cancer on HIV-seropositive women and women, in general, has been difficult to quantify in Zimbabwe and developing countries as a whole and even more difficult to put on the agenda of health policymakers. This research not only produced information that will help and support Zimbabwe initiate and develop a cervical cancer primary prevention tool especially for young people, but also offered a lens to potential strategies on how to improve and integrate the management of cervical cancer among HIV-seropositive women into already existing services. Integration of cervical cancer services into HIV programmes to offer a 'one-stop' approach designed to improve patients' convenience and utilisation of cervical cancer services such as screening and early treatment.

In addition, this research has implications on the significance of the findings regarding the knowledge of young people on cervical cancer, HPV, cervical cancer screening and HPV vaccination in Zimbabwe, namely disjuncture with the prevailing global policy approach. This information might be important to Zimbabwe in structuring an inclusive cervical cancer policy especially in light of the recently launched Mass HPV Vaccination among young girls aged 9 to 14 years old. The generated data can also serve as baseline information for future monitoring and evaluation of cervical cancer prevention and HPV vaccination initiatives and programmes.

When reliable baseline data that reflect the knowledge and attitude of young people towards cervical cancer has been produced, it may enable cervical cancer stakeholders to develop and package appropriate and targeted prevention programmes for young people. Baseline synthesised evidence on the current management of cervical cancer in HIV-seropositive women can be important in informing the prioritisation of cervical cancer services towards this group and how future plans can be modelled to improve impact. The study also highlighted other public health areas around cervical cancer prevention and treatment that require further

research in Zimbabwe and other Sub-Saharan African countries such as formulation of new and advanced cervical cancer screening and treatment tools for HIV-seropositive women.

1.7 Organisation of the thesis

This thesis is organised into the following chapters:

Chapter 1. Presented the introduction, contextual background, motivation for this study and a summary of the research's potential impact.

Chapter 2. Describes the literature review, theoretical frameworks guiding the cross-sectional component of the study, rationale and goals of this thesis in detail. It includes a short description of how the research was to be conducted.

Chapter 3. Describes in detail the methodology of the two systematic reviews and the cross-sectional survey and it outlines the steps taken for the reviews and how data was collected in the field.

Chapter 4. Describes the results as follows

- Section 4.1: Details the results of the systematic review on the prevention of cervical cancer in HIV-seropositive women in developing countries
- Section 4.2: Details the results of the systematic review on the treatment of cervical cancer in HIV-seropositive women in developing countries
- Section 4.3: Details the results of the cross-sectional survey on the knowledge, attitude and practices of young people towards cervical cancer, screening, HPV and vaccination

Chapter 5. Interprets and discusses the results of the systematic reviews and the cross-sectional survey and highlights the gaps within the current prevention and treatment methods of cervical cancer in HIV-seropositive women as well as the lack of cervical cancer primary prevention

tools. The chapter also highlights the knowledge, attitude and practices of young people towards cervical cancer risk factors, prevention and treatment.

Chapter 6. Summarises the core results of the study and suggests recommendations that policymakers, health care providers and researchers can uptake in an effort to reduce the morbidity and mortality due to cervical cancer.

Appendices. The appendices section shows publications that have emanated from this work as well as the systematic review tools (full-text screening form, data extraction form, and quality assessment checklists), cross-sectional data collection questionnaire and different approval and ethical letters.

CHAPTER TWO: LITERATURE REVIEW

Note: Some of the literature reviews in this chapter have been published in BMC Systematic Reviews Journal (see Appendix 19).

2.1 Introduction

Chapter two of this thesis is an overview of the two theoretical frameworks for cervical cancer research, literature review of cervical cancer, HPV, cervical cancer screening or prevention, cervical cancer treatment and sociodemographic factors of young people and their knowledge, attitudes and practices towards cervical cancer. The articles that were utilised for this literature review were searched from the following electronic databases: PubMed, MEDLINE, CINAHL, Embase, Cochrane Library and Centre for Reviews and Disseminations. A number of key words: cervical cancer, prevention, screening, treatment, HPV, HIV, young people, knowledge, attitude, practices, were combined differently to find the articles which were used to construct the literature review.

2.2 Theoretical framework of cervical cancer research

Developing appropriate research to answer critical research questions and produce suitable findings that can have an impact on policies, interventions and health behaviours, requires studies to be modelled around theoretical frameworks. As indicated in the overview section, cervical cancer incidence, morbidity and mortality is high in Zimbabwe and in addition, there is general lack of health education and health promotion for cervical cancer[1]. To be able to answer the questions pertaining to the epidemiology and knowledge concerning cervical cancer in Zimbabwe and appreciate the current cervical cancer management in developing countries, two theoretical frameworks, namely, the Health Belief Model (HBM) and the social ecological model (SEM), were used to provide the foundations of this study. Both the HBM and the SEM believe that individual health behaviours, knowledge and health seeking perceptions are influenced by the environment and sociodemographic characteristics[6]. These two theoretical

frameworks guided the designing of the research, its methodology including data collection instruments and data collection process, recommendations and discussion.

In a study among adolescents, findings suggested that health behaviour towards a disease, like cervical cancer in this case, is governed by what is available in terms of strategies and structure to reduce the disease occurrence and improve people's beliefs and knowledge about the disease[18]. The HBM has evolved and is now based on six constructs, which are, perceived susceptibility, perceived severity, perceived beliefs, perceived barriers, cues to action and self-efficacy[6,7] (see Figure 2.1). The constructs of the HBM can help predict behaviour in cervical cancer screening as well as how the application of the HBM can be used to design a health behaviour improvement intervention[19]. The scope and application of the HBM is suitable for understanding cervical cancer epidemiology and knowledge in Zimbabwe. This is because the HBM offers a framework to understand preventative health behaviours such as health promotion (e.g. being faithful to one sexual partner, use of condoms, delayed sexual debut), health risk (HPV, HIV, smoking, herbs) behaviours and contraceptive and vaccination practices. Lastly, the HBM was used to assess the health services use behaviours, which in this research involved young people's attitudes, beliefs and practices toward seeking cervical cancer knowledge, cervical cancer screening and vaccination.

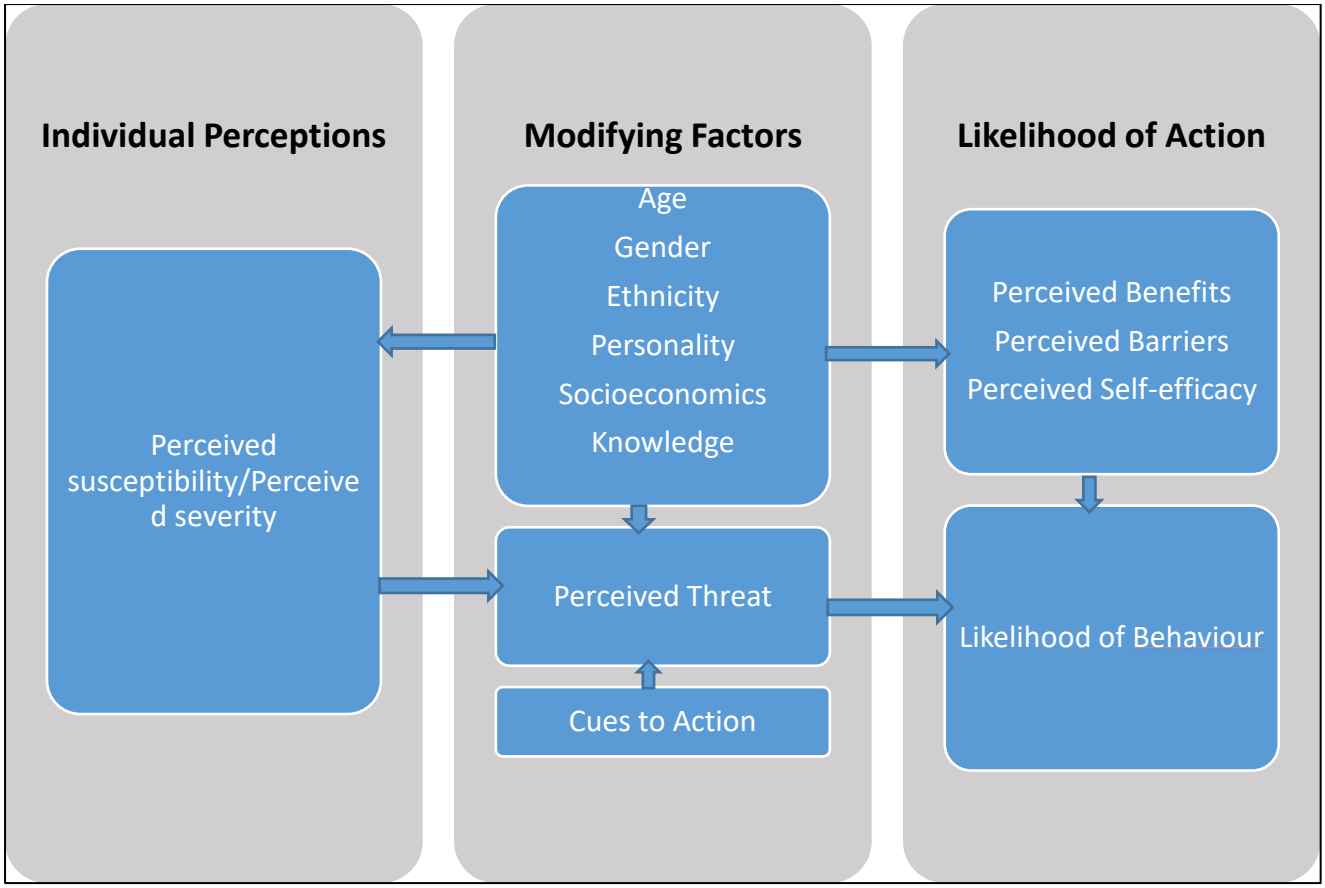

Figure 2.1: Health Belief Model in Cervical Cancer

Adapted from Source: Stretcher V. Rosenstock I.M. (1997). The Health Belief Model. In Glanz K. Lewis F.M. Rimer B.K. (Eds). Health Behaviour and Health Education: Theory, Research and Practice. San Francisco: Jossey-Bass

The SEM states that individual behaviour is influenced by a number of different levels and that social environment and an individual have a bi-directional relationship[6]. The SEM has seven influencing levels, which are, the intrapersonal, interpersonal, organisation, public policy, physical environment, community and culture[20] (see Figure 2.2). In applying the SEM in this study, the seven levels can affect an individual's health seeking behaviour, knowledge, attitudes and beliefs pertaining to cervical cancer, its risk factors, prevention and its management. Evidence from an integrated screening and evaluation programme suggested that using the SEM for cervical cancer screening can help more women to be screened and this can lead to improved health outcomes[21]. This was supported by the Centers for Disease Control and Prevention (CDC), which explained how the SEM could be adapted to facilitate both the

provision of cervical cancer screening services and a population-based screening regime[22]. For this study, intrapersonal level related to an individual's knowledge, attitude and beliefs towards cervical cancer. While interpersonal level looked at the way family, friends and media have had an influence on the individual's health behaviour and knowledge of cervical cancer.

Thirdly, the organisational level assessed the role of the health services facilities and educational facilities in Zimbabwe in the cervical cancer matrix. The physical environment looked at the issues like availability of cervical cancer screening and vaccination services, distance people live from a health facility and whether they live in rural or urban settings and how these affect cervical cancer epidemiology and knowledge in Zimbabwe. Policies and laws that regulate and support health and in particular cervical cancer prevention, screening and vaccination were explored through the public policy level. Culture in the view of norms, values, standards and patriarchal system especially in the African context and how it shapes an individual's health behaviour and knowledge was also assessed under the social ecological model.

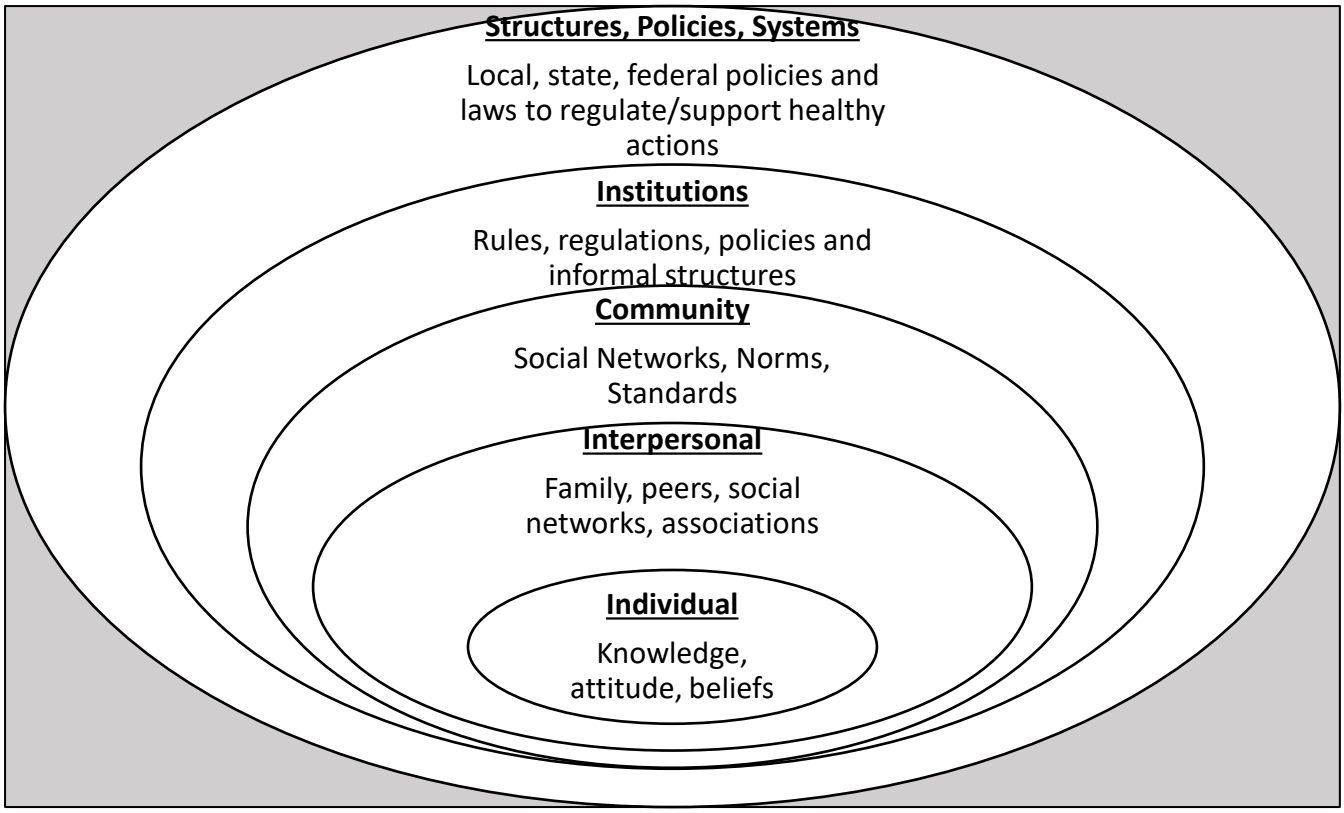

Figure 2.2: Social Ecological Model in Cervical Cancer Research

Source: Simons-Morton, B., K. R. McLeroy, and M. L. Wendel. 2012. Behavior theory in health promotion practice and research. Burlington, MA: Jones & Bartlett Learning

Both these models, the HBM and the SEM provided the foundations on which this research was formulated to enable the answering of research questions that relate to cervical cancer epidemiology and knowledge in Zimbabwe. The models were also applied in the interpretation of the research findings to fit and relate to the Zimbabwean context.

2.3 What is cervical cancer?

Cervical cancer is a medical condition where there is malignant neoplasm arising from cells originating in the *cervix uteri*[23]. Globally, cervical cancer has become the second most cancer affecting women with about half a million cases and almost 280 000 deaths annually[8]. A significant number (approximately 85%) of these annual deaths, occur in the developing world[8]. A number of risk factors increase a woman's chance of getting cervical cancer and the most important is HPV. HPV is highly infectious and easily transmissible through sexual

activity[24]. There is a strong causal relationship between cervix infection with high-risk HPV types, most commonly HPV type 16 and 18, and development of cervical cancer[25]. Several other risk factors such as being immunocompromised/suppressed (HIV-positive), chlamydia infection and multiple full-term pregnancies increase a woman's chance of developing cervical cancer[2,26]. Modifiable factors such as long-term use of oral contraception, smoking, age of first sexual intercourse and having sex with multiple partners also contribute to cervical cancer risk[27]. Poverty and health inequity have also been associated with cervical cancer morbidity and mortality in developing countries[14].

2.4 Epidemiologic classification of HPV types associated with cervical cancer

Most cervical cancer cases are diagnosed in women above 40 years old and are linked to HPV infection[24]. HPV is aetiologically linked to cervical cancer and strong biological and epidemiological evidence suggest it is necessary to be infected with HPV to develop cervical cancer[28-29]. There are over 150 related types of HPV and about 40 of these types are transmitted through sexual activity[30]. Infections due to HPV occur in the young women mostly and 70% of these infections disappear spontaneously and without medication within a year and 90% within two years[24]. However, in cases where the infection persists over a long period, it can be a cause of cancerous lesions, causing over 90% of cervical cancer cases[31-32].

Out of the 150 reported HPV types, 40 HPV types are transmitted through sexual activity and these have the potential to cause genital infection[30]. This was supported by evidence in different parts of the world that have indicated that not all HPV types are associated with cervical cancer[31,33-34]. Certain types of HPV have been identified to be the cause of intraepithelial neoplasm and invasive cervical cancer.

Pooled data from eleven case-control studies done in nine different countries has classified genital HPV into two broad categories namely high-risk types (those frequently associated with

invasive cancer) and low-risk types (those associated with causing genital warts[35]). This classification has been based on molecular epidemiology and the oncogenic threat of the HPV type. The pooled data identified 15 HPV types as high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82). Of these 15 HPV types, eight were identified as the most common in descending order (16, 18, 45, 31, 33, 52, 58 and 35). HPV 16 (58.9%) and HPV 18 (15.0%) were the most common HPV types[35]. The two 'high risk' HPV types 16 and 18, causes 70% of all global cervical cancer cases[8]. On the other hand, the pooled data identified 12 HPV types as low-risk types (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 and CP6108)[35].

2.5 Cervical cancer pathogenesis, types and stages

For cervical cancer to develop there should be a persistent infection with oncogenic HPV types and the average period between HPV infection and cervical cancer development may be up to around 20 years[24,36]. There are two main types of cervical cancer namely adenocarcinoma and squamous cell carcinoma. Squamous cell carcinoma is the most frequent one and it accounts for over 80% of all cervical cancer cases, with the remaining being cervical adenocarcinoma[24]. However, before it becomes squamous cell carcinoma or cervical adenocarcinoma, women infected with oncogenic HPV first develop pre-cancerous lesions.

2.5.1 Pre-cancerous cervical abnormalities

When infected with oncogenic HPV, the normal cells in the cervix first develop precancerous changes that might progress to cervical cancer[37]. These pre-cancerous lesions are graded and grouped as cervical intraepithelial neoplasia (CIN), squamous intraepithelial lesions (SIL) and dysplasia[37].

- CIN 1 – resolve mostly without treatment in the majority of the cases[38].

- CIN 2 and 3 – these develop from a small proportion of those with CIN 1. CIN 2 is moderate and CIN 3 is severe. CIN 1 can also progress to precancerous lesions called adenocarcinoma in situ (AIS).
- If women with CIN 2 and 3 are untreated, they have a high chance of developing squamous cell cancer and those with untreated AIS are prone to develop cervical adenocarcinoma[15].

2.5.2 Cervical cancer – staging

Cervical cancer progression is grouped into five stages; from stage 0 to stage 4 (see Table 2.1). The diagnosis of cervical cancer involves tests to determine its stage (how far the cancer has spread) and what kind of treatment is required at that particular point.

Table 2.1: FIGO staging of cancer of the cervix uteri (2018)

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm
IA1	Measured stromal invasion <3 mm in depth
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than Stage IA), lesion limited to the cervix uteri
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	Invasive carcinoma ≥4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma <4 cm in greatest dimension
IIA2	Invasive carcinoma ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or para-aortic lymph nodes
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumour size and extent (with r and p notations)
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. (A bullous oedema, as such, does not permit a case to be allotted to Stage IV)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

Source: Bhatia N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. FIGO Cancer Report 2018. Int J Gynecol Obstet 2018; 143(2): 22-36 https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1002/ijgo.12611

2.6 Cervical cancer screening and vaccination

A number of cervical cancer screening methods are available and these methods are classified into visual inspection tests, cytological tests, and diagnostic and treatment modalities (colposcopy, cone biopsy, cryotherapy, loop electrosurgical incision procedure (LEEP) and HPV DNA tests)[39]. Among cytological tests, there is the Papanicolaou smear test (Pap smear or glass slide cytology) and the liquid based cytology. Under visual inspection tests, there is the visual inspection with acetic acid and cervicoscopy (VIAC) and the visual inspection with Lugol's iodine (VILI)[40]. With an incubation period of about 10 to 20 years from infection with

HPV to development of cervical cancer, screening, tracking and detection of cervical cancer is possible[41].

Comprehensive cervical cancer screening can prevent cervical cancer morbidity and mortality and while Pap smear coupled with treatment has reduced cervical cancer deaths in high-income countries, its effectiveness is still low in lower-resource countries[42]. Invasive cervical cancer has decreased by 80% in the United States since adoption of Pap smear over five decades ago[43]. In developing countries, routine cervical cancer screening using Pap smear has not been feasible and has faced a number of implementation barriers, chief among others being, high costs, lack of trained personnel, and lack of infractructure[44]. High-risk HPV (hrHPV) testing, which has a high sensitivity, is another screening tool that has been utilised in the developed countries[45-46]. However, hrHPV testing is relatively expensive and not widely used in developing countries. Developing countries have focused more on using WHO recommended alternative screening tools in the form of visual inspection tests (VIA and VILI) and in some instances, coupled with cryotherapy[47-48]. Regardless of these recommendations and guidelines from WHO, screening algorithms and available screening services vary among the developing countries due to the above-mentioned implementation challenges. The impact of different methods to detect and prevent cervical cancer continue to be low in developing countries and health inequity is a major factor contributing to high cervical cancer incidence[14]. Per hundred thousand population among women with cervical cancer, disability-adjusted life years (DALYS) stands at 641 per 100 000 in SSA, 355 per 100 000 in Latin America and lowest in Australia and New Zealand at 58 per 100 000[14].

2.7 Cervical cancer treatment

There are a number of treatment modalities for cervical cancer, namely: chemotherapy, surgical management and radiation therapy[13,49-50]. Treatment modalities for precancerous lesions and cervical cancer are based on the stage of the lesions and available resources. According to the

American Cancer society, surgery or radiation or a combination with chemotherapy are the treatment choices for the early stages of cervical cancer, whilst radiation and chemotherapy are for late advanced cervical cancer[50]. Surgery (radical hysterectomy or lymphadenectomy) performed by gynaecologists is a better option to chemoradiation therapy in the early stages of cervical cancer and this has been seen to be effective[50]. Locally advanced cervical cancer is treated by radiation therapy (brachytherapy, external beam radiation therapy) or concurrent cisplatin based-chemotherapy[51]. Evidence generated in Western countries has indicated that concurrent treatment with chemo-radiation therapy is more effective as compared to radiation alone[52]. In terminal or late advanced stages, cervical cancer patients are offered palliative care integrating psychosocial and physical needs and appropriate opioid analgesics[53].

In sub-Saharan Africa, treatments like radiation therapy and other surgical procedures are not fully utilised because of lack of equipment and qualified personnel to carry out the procedures[54]. Most developing countries lack skilled surgeons to carry out radical surgery for advanced cervical cancer and this has left cervical cancer patients with few treatment options. In cases where surgeons are available, surgery is expensive and out of reach of many, who happen to be poor[55]. In addition, in developing countries due to health inequity, unavailability of quality affordable healthcare services and lack of resources, have made access to radiotherapy and chemotherapy difficulty, further limiting treatment options[56].

2.8 Cervical cancer and HIV in developing countries

With the increase in cervical cancer morbidity and mortality in developing countries, concern has shifted to how much can be done to prevent this public health challenge especially in those who are immunocompromised. With the advent of HIV in most of developing countries especially those in sub-Saharan Africa, the incidence and burden of cervical cancer is increasing[2,9,57-58]. The advent of HIV/AIDS in most developing countries has resulted in high cervical cancer prevalence and because of this; cervical cancer has been classified as an AIDS-

defining disease[2,58]. HIV-seropositive women have been found to be at higher risk of HPV infection due to their immune compromised status and they are 2 to 12 times more likely to develop cervical precancerous lesions that lead to cervical cancer than HIV-negative women[2]. Rapid progression of the disease among those infected with HIV have been documented[42]. This might be important because it means women with HIV should have more frequent screening with shorter intervals between screening dates.

Cervical cancer screening is important in reducing morbidity and mortality in HIV-infected women and a number of screening methods are available. However, regardless of the available screening methods and considerable evidence in reducing the burden of cervical cancer, epidemiological and health systems challenges and constraints still exists in most developing countries that make it difficult for some cervical cancer screening strategies and initiatives to be available[13]. In addition, there is lack of opportunistic or organised and systematic population based screening among HIV-seropositive women due to fewer resources, resulting in uncoordinated screening with any available screening method. With the introduction of mass HPV vaccination for young girls in some developing countries, opportunities to offer the vaccine to HIV-positive middle-aged women through HIV health programmes exist. The safety and immunogenicity of HPV vaccine is almost comparable in HIV-positive and HIV-negative women[13,59]. Offering HPV vaccination, as primary cervical cancer prevention to HIV-positive women might reduce cervical cancer incidence and morbidity.

Despite a number of evidence-based guidelines, strategies and research on cervical cancer screening or prevention in low-resource settings, slow progress in implementation of these guidelines due to lack of implementation experts has become a public health challenge that requires urgent solutions to mitigate the morbidity and mortality due to cervical cancer. There is little rigorous synthesised evidence on which cervical cancer screening methods are being used for HIV-seropositive women, if these current screening methods are the same for HIV-

negative women and if these screening methods are effective for HIV-seropositive women. The review aims to answer the following questions: What are the screening methods that are used to prevent cervical cancer in HIV-seropositive women in developing countries? Are these the same screening methods that are used for HIV-negative women? Are the screening methods effective in HIV-seropositive women?

In developing countries, especially sub-Sahara Africa, many women with cervical cancer have no access to radiotherapy, further limiting their treatment options. However, little or no information exist that has shown that any of the current treatments are effective compared to other treatments when it comes to treating cervical cancer in HIV-seropositive women. There is lack of evidence based guidelines and strategies for treatment of cervical cancer in HIV-seropositive women in most developing countries. Coupled with this, there is little rigorous evidence on the global epidemiology of the treatment of cervical cancer in HIV-seropositive women[54]. The following questions require answers: What are the treatment methods that are being used to treat and manage cervical cancer in HIV-seropositive women in developing countries? Are these the same treatment methods that are being used for HIV-negative women? Are the treatment methods effective in HIV-seropositive women?

2.9 Zimbabwe's current situation

Despite data on cervical cancer and its risk factors being limited in Zimbabwe, the incidence and burden of cervical cancer is growing due to high HIV prevalence, resource constraints and a weak underfunded healthcare system. According to the Zimbabwe National Cancer registry, cervical cancer is responsible for 33.5% of overall recorded cancer cases[60]. The WHO indicated that about 2000 women are diagnosed with cervical cancer every year in Zimbabwe and almost 69% of them die[61]. Most women in Zimbabwe continue to face challenges in accessing regular sexual and reproductive health care.

The political and economic problems that have affected Zimbabwe for the past 18 years have seen funding for health care being limited. HIV/AIDS, TB, cholera and malaria have been the government's priority during these difficult times and cervical cancer funding has remained insignificant. In as much as Zimbabwe has undertaken cervical cancer screening, mostly for the 21-49 year age group, resource constraints have limited the decentralisation of cervical cancer cases. The current system of cervical cancer screening and management is based largely on the secondary and tertiary health institutions and facilities. At primary health care level, cervical cancer screening is first offered at district hospitals and city council polyclinics, with fragmented treatment only available at tertiary level, hence this might be contributing to late diagnosis and high mortality rate.

On the other hand, recent years have witnessed an increase in risky lifestyle behaviour including early onset of sexual activity, multiple sexual partners and age-disparate relationships among the 15 to 24 year age group, resulting in high HIV incidence and placing young women at risk. HIV incidence for young women between the ages of 15-24 years is reported to be twice as high in Zimbabwe and four times higher in South Africa as compared to young men of the same age-group. In addition, there is insufficient knowledge about sexual reproductive health including cervical cancer among the young people.

Key factors that continue to underlie the failure to enhance cervical cancer management in Zimbabwe include legislative challenges, inadequate cervical cancer information system and inadequate resources, among others[16]. Zimbabwe does not have a cancer primary prevention strategy that focuses on cancer risk factors. Lack of information and knowledge about cervical cancer are some of the reasons contributing to underutilisation of screening services, late diagnosis of the condition, and a high mortality rate[60].

Secondly, there is lack of cervical cancer prevention policies even in light of the newly launched Mass HPV Vaccination Programme for young girls. The National Cancer Prevention And Control Strategy For Zimbabwe 2013 – 2017, which encompassed cervical cancer prevention and management, was not fully implemented due to inadequacy of cancer legislation and resource constraints. These legislation and policy challenges might be contributing to the fragmentation of cervical cancer service provision and failure to prevent 'silo' operation among different partners within the sexual reproductive health management space. Despite the introduction of the Mass HPV Vaccination Programme in May 2018, the country continues to lack policy guidance on how such initiatives will be sustained and made available to meet the Ministry of Health and Child Care's mission of providing equitable access to quality health care to everyone.

Lastly, Zimbabwe remains a patriarchal society and most men continue to make decisions on the health of women, from providing for money for hospital fees to deciding if it is necessary for women to seek medical attention[16]. Men continue to be side-lined in women's' health prevention programmes and this has fuelled their passive nature towards health seeking behaviour[60].

2.10 Cervical cancer prevention in Zimbabwe

Pap smear has been available in Zimbabwe for quite some time and offered in both government and private hospitals. However, Pap smear has continued to be underutilised because it is expensive for the majority of Zimbabweans, mostly centralised in major cities because of lack of proper infrastructure and lack of knowledge and awareness[17].

With the support of United Nations Population Fund (UNFPA), the Ministry of Health and Child Care (MOHCC) is offering cervical cancer screening through VIAC at several hospitals namely Mpilo, Parirenyatwa, United Bulawayo Hospital and Masvingo. In Harare, other

centres such as Spilhaus, Newlands clinic and city of Harare clinics, offer these cervical cancer screening services as well. Although VIAC method is free (in some cases it is charged $5 to $15), the services cater for women 21 years old and above and have been centralised at the major hospitals which are available in urban areas.

Cervical cancer vaccination started to be administered in western countries in 2007 for girls and women between 9 and 26 years[62]. The government of Zimbabwe through the Ministry of Health and Child Care (MoHCC) agreed and approved HPV vaccination in 2009. However, financial constraints and failure to meet the requirements (ability to vaccinate an adolescent population) required by the Global Alliance on Vaccines and Immunisations (GAVI) delayed the introduction of the mass HPV vaccination until May 2018. As of 2015, only two private centres were offering HPV vaccination in Zimbabwe at a cost that very few people (and young people) could afford considering the present economic climate and challenges.

2.11 Young people in Zimbabwe and cervical cancer

According to the World Bank 2014 report, the standard of living in Zimbabwe has fallen far below the poverty datum line with an average person surviving on about $1.16 per day[63]. This situation has forced many young women to turn to prostitution and other high risk sexual practices with older men to earn a living and take care of their siblings. Becoming sexually active early and having multiple age-disparate sexual partners have fuelled the spread of HIV especially among young women that is disproportionate to their male peers[64].

Engaging in risky sexual behaviour and insufficient knowledge about health issues remain at alarmingly high levels among young people aged between 15 to 24 years old[65]. This was supported by findings that showed that condom use among the 15 to 24 year olds in SSA was only at 57% for young men and 37% for young women, which was below the 95% target advocated by UN General Assembly Special Session on HIV and AIDS in 2001[66]. In 2015,

17% of young women aged 15-19 years in Zimbabwe reported having had sex with a man 10 years older than themselves in the past 12 months. In addition, HIV prevalence among young people in Zimbabwe increases with age, from around 3% in women aged 15-17 years to 14% among the 23-24 year olds. Whilst among young men, the HIV prevalence rises from about 2.5% to around 6% among the 23-24 year olds[67]. However, only 64% of young women and 47.5% of young men have ever been tested for HIV[68].

Sexual behaviour of both men and women is a risk factor for cervical cancer. Though they do not develop cervical cancer, assessing knowledge, attitude and practices of young men can be vital if a coordinated inclusive strategy towards prevention of cervical cancer is to be formulated as advocated by World Health Organisation (WHO) in 2009. In addition, involving men in cervical cancer initiatives such as the HPV vaccination has a cost-benefit relationship that makes it necessary for them to be incorporated in cervical cancer prevention strategies[69].

Knowledge and awareness of cervical cancer and HPV are consistently low across developing countries and such lack of knowledge provides a challenge to the implementation of cervical cancer programmes and the new mass HPV vaccination drive[70]. Evidence among women aged 18 to 44 years old indicated that the majority of women are unfamiliar with cervical cancer, HPV, vaccination and screening and that they face a number of barriers accessing cervical cancer screening services[71-72]. Sources of information where people get to know about cervical cancer are still limited in developing countries. For example, a study suggested that vaccinated girls were likely to know about cervical cancer if their mothers had previously been screened for cervical cancer[73]. This finding suggests that, there is some sort of passing down of health knowledge within families especially when parents have utilised health services. However, in a country like Zimbabwe where over 80% of rural women had no previous knowledge about

cervical cancer[17], such passing down of knowledge from parents to children is likely not to exist. Parents' knowledge and attitudes towards cervical cancer is one of the parameters that can enhance or prevent full implementation of cervical cancer prevention strategies in the young. In the US, it was reported that parents had a tendency of refusing vaccination of their children towards a disease that is sexual transmitted[74].

Although women talk with their children about sexual and reproductive health issues, evidence suggests that women have limited knowledge about cervical cancer[17], HPV, vaccination as well as having reservations on the long-term effect of the HPV vaccination. This poses a scenario where a culturally conservative people like Zimbabweans might not feel obliged to discuss HPV, cervical cancer, screening and vaccination with their children. With the nature of our culture where sexuality issues are not discussed openly in families, the issue of how much knowledge and awareness children get from parents needs to be measured. Issues to do with culture, barriers to access health care and lack of awareness of the benefits of screening and vaccination have been highlighted as some of the issues associated with sexual and reproductive health among the young people in Zimbabwe.

Among young people, a number of questions require answers. Do young people know about cervical cancer? What are their beliefs and attitude towards cervical cancer risk factors, screening and HPV vaccination? Do they know how and where to access cervical cancer services in the country? How do young people feel about cervical cancer screening? Do seeking cervical cancer services paint them differently among their peers? What can be done from their point of view to create a youth friendly environment as a way of promoting cervical cancer screening and vaccination? How can cervical cancer services be easily available and acceptable among the young people?

2.12 Cervical cancer in South Africa: can Zimbabwe learn something?

Cervical cancer is the second most common cancer among South African women and continues to be an important public health problem[75]. Several studies on HPV, HIV, cervical cancer, screening and vaccination have been done in South Africa to the effect that their cervical cancer epidemiology includes the understanding of HPV history in South Africa, HPV prevalence among HIV seropositive women and challenges to screening[75]. This offers an opportunity to compare what has been done in South Africa to what we currently know of Zimbabwe with the view to identify what needs to be done to understand cervical cancer epidemiology in Zimbabwe. The studies that have been done in South Africa and the information generated, provides Zimbabwe with an opportunity to know where research should be prioritised in trying to understand the epidemiology of cervical cancer.

However, considering the number of studies and research done in South Africa, there remain challenges with cervical cancer screening, vaccination and risk factors including HPV, HIV and lifestyle factors because of the lack of knowledge of the disease and risk factors.

2.13 Chapter two summary

Two theoretical frameworks, the Health Belief Model and the Social Ecological Model, are going to be used to guide the research process to answer the questions pertaining to the epidemiology and knowledge concerning cervical cancer in Zimbabwe.

HPV is aetiologically linked to cervical cancer and strong biological and epidemiological evidence suggest that persistent infection with oncogenic HPV is necessary to develop cervical cancer. There are two main types of cervical cancer. The squamous cell carcinoma is the most frequent one and accounts for over 80% of all cervical cancer cases, with the remaining being cervical adenocarcinoma. The adverse effects of HIV in most developing countries has coincided with the increase in incidence and burden of cervical cancer. HIV-positive women are at higher risk of developing cervical cancer due to their immunocompromised status.

Although cervical cancer prevention has reduced morbidity and mortality in developed countries, epidemiological and health systems challenges still exists in most developing countries that make it difficult for some screening strategies to be fully implemented. Developing countries are focusing on using WHO recommended alternative screening tools in the form of VIA or VILI and in some instances coupled with cryotherapy. Treatment for cervical cancer in developing countries is determined by the available resources and expertise and treatment options are few. Cervical cancer prevention strategies should priorities HIV-seropositive women and young people because of their unique role in the cervical cancer web.

CHAPTER THREE: METHODOLOGY

Note: Some of the methodology in this chapter has been published in BMC Systematic Reviews Journal (see Appendix 19).

3.1 Introduction

This chapter explains in detail the design of the methodological (two systematic reviews and a cross-sectional survey) approach, laying out in detail the protocols for the systematic reviews, and how sample size, sampling procedure, data collection process and data analysis for the cross-sectional survey, was conducted. The chapter is laid out as follows:

- Section 3.2 explains the protocol of the systematic review on prevention of cervical cancer among HIV-seropositive women,
- Section 3.3 explains the protocol of the systematic review on treatment of cervical cancer among HIV-seropositive women and
- Section 3.4 details the methodology of the national cross-sectional survey on knowledge, attitude and practices of young people on cervical cancer, screening, HPV and vaccination.

3.2 Protocol for the systematic review on prevention of cervical cancer in HIV-seropositive women through screening from developing countries

The development and reporting of this protocol was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols (PRISMA-P) statement (see Appendix 1) and the systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[76] and was registered with the PROSPERO database (CRD42018095702)[77]

3.2.1 Studies' eligibility criteria

Studies were included if

- Cervical cancer prevention methods for HIV-seropositive women (such as pap smear, visual inspection with acetic acid, HPV DNA testing and HPV vaccination among others) were key outcomes
- HIV and cervical cancer prevention modalities were considered being independent and outcome variables respectively
- Description, effect or impact of the prevention modality on HIV-seropositive women was an outcome
- Published in peer-reviewed journals
- Done in or for countries or regions considered to be developing countries by United Nations[78]
- They were randomised controlled trials and observational study designs – prospective cohorts, retrospective cohorts, case-control and cross-sectional
- Reported in English language
- Prospective cohort studies had a defined length of follow up. Length of follow up was used to assess for the quality of the outcomes.

Studies were not excluded based on length of follow up. However, follow up rates were used to give scores to the quality of the outcomes. Follow up rates of less than 60% were considered as having limited validity especially when the reasons for loss were related to both exposure and outcome status[79]

In cases of studies done across countries, that are developed and developing, the team extracted results for developing countries from these where possible and contacted study authors for more information. All studies were included and sample sizes were used to assess quality and inform interpretation of findings. The reviewers' assumptions were that studies with smaller samples might not provide additional value in terms of high quality evidence[80]. Reviews, studies looking at cervical cancer in general and those with unrepresentative samples were excluded. Unrepresentative samples (looking at HIV positive women, controls and sampling criteria) were identified through performing non-parametric tests on geographical and demographical representation of the sample against that of the population.

3.2.2 Search strategy

Two independent reviewers (WM and TC) guided by a protocol searched PubMed (via the PubMed/MEDLINE interface using the "PICO" option), CINAHL (via the EBSCO interface using key words), Cochrane (via The Cochrane Library using MeSH terms and qualifiers), Embase and MEDLINE (via the OvidSP interface) using key words and supplementary free-text terms (see Table 3.1) until January 2018. Truncation commands (root word) and proximity operators (words which will be within a chosen distance of each other) and Boolean logic operators (OR and AND) were used as well (see Table 3.2). Search terms as follows: (cervical cancer or cervical neoplasms or cervical carcinomas) AND (prevention or screening or Pap smear or VIA) AND (developing countries or underdeveloped countries or low-income countries) were used specifically for each database (see Appendix 2). To improve the efficiency

of the final search, preliminary trials with search terms were conducted. Citation and reference tracking was conducted to search additional papers to add to the electronic database search.

Table 3.1: Medline and Embase search strategy via OvidSP

Search Terms	
1.	cervi* canc*.mp. [mp=title, abstract, full text, caption text]
2.	cervi* neoplas*.mp. [mp=title, abstract, full text, caption text]
3.	cervi* carcinom*.mp. [mp=title, abstract, full text, caption text]
4.	cervi* dysplas*.mp. [mp=title, abstract, full text, caption text]
5.	cervi* intraepithelial neoplas*.mp. [mp=title, abstract, full text, caption text]
6.	prevent* or screen*.mp. [mp=title, abstract, full text, caption text]
7.	pap smear* .mp. [mp=title, abstract, full text, caption text]
8.	colposcopy.mp. [mp=title, abstract, full text, caption text]
9.	hpv adj3 vaccin*.mp. [mp=title, abstract, full text, caption text]
10.	HIV positive.mp. [mp=title, abstract, full text, caption text]
11.	hiv seropositiv*.mp. [mp=title, abstract, full text, caption text]
12.	hiv.mp. [mp=title, abstract, full text, caption text]
13.	developing countr*.mp. [mp=title, abstract, full text, caption text]
14.	underdeveloped countr*.mp. [mp=title, abstract, full text, caption text]
15.	low income countr*.mp. [mp=title, abstract, full text, caption text]
16.	low resource countr*.mp. [mp=title, abstract, full text, caption text]
17.	low resource setting*.mp. [mp=title, abstract, full text, caption text]
18.	developing countries.mp. [mp=title, abstract, full text, caption text]
19.	1 or 2 or 3 or 4 or 5
20.	6 or 7 or 8 or 9
21.	10 or 11 or 12
22.	13 or 14 or 15 or 16 or 17 or 18
23.	19 and 20 and 21 and 22

Table 3.2: Techniques used in the online databases search

Techniques	Description	Example
Free-text synonyms of keyword search	All known synonyms of the keyword in both British and US spellings	Cervical cancer synonyms: cervical carcinomas, cervix neoplasms, cervical intraepithelial neoplasia, cervix dysplasia etc.
Truncation commands	Using the root word to capture alternative word endings	Cervi* carcinom* searches for words such as cervical carcinoma, cervix carcinomas etc.
Proximity operators	Operators used Adj3 in OvidSP interface	hpv adj3 vaccin*
Boolean logic operators	'OR' and 'AND' were the two commands used. 'OR' is used to locate articles with at least one of the search terms. 'AND' is used near the end of a search so as to combine results of different search concepts.	treat* or therap* OR radiation adj3 therap*. (treat* or therap* OR radiation adj3 therap*) AND (HIV positive OR hiv seropositiv* OR hiv) AND (developing countr* OR underdeveloped countr*)

3.2.3 Study selection

The initial search of the databases yielded 2557 results and an additional two studies were identified through citation and reference tracking to make a combined 2559 articles. Two independent reviewers (WM and SF) conducted the screening process to identify eligible studies and reasons for excluded studies were documented. Disagreements and other issues related to the screening process were resolved as reported in the protocol. Removal of duplicates and screening of title and abstracts excluded 2212 articles. An additional 198 articles

were further excluded because of not being relevant to the topic. The remaining 149 articles were reviewed in full text (see Appendix 3) and 124 studies were excluded for not meeting the eligibility criteria. Twenty-five articles met the eligibility criteria and were included for final analysis.

3.2.4 Data extraction

The primary reviewer (WM) and TC double extracted the data. The data extraction form (see Appendix 4) was piloted on a few selected studies and adjusted accordingly for its appropriateness. The following content from the included 25 studies was extracted: title of the study, author, publication year, study design, study setting (country/region), sample size, exposures and outcomes and all results including statistics. Three additional team members, SF, BGB and ES, assessed the extracted data to ensure accuracy and inconsistencies were discussed and resolved through consensus. Frequency tables were used to summarise the results.

3.2.5 Quality assessment

The quality of the included studies was assessed using a combination of a modified version of the Newcastle-Ottawa Quality Assessment Scale[81] (see Appendix 5) and the NIH Study Quality Assessment Tools for observational cohort cross-sectional case-control and before-after studies[82]. The following: focus of research, key findings, study design, length of follow-up and representativeness of participants, were used to ascertain quality. For an easy quality assessment process, studies were categorised into three groups, namely randomised controlled-trials, observational studies with control group(s) and observational studies without control group(s). Outcome measures were assessed based on whether the articles had a predefined outcome measure and if any cervical cancer prevention method was explored or its application was discussed. Two independent reviewers (WM and BGB) carried out the quality assessment process and discrepancies that arose were resolved through discussion with other team

members. The average score of the two reviewers (WM and BGB) on both the quality assessment tools became the quality score for each study, with zero being very low quality and five being high quality.

For RCT studies, assessment was based on whether (1) randomization of participants was reported, (2) all participants who entered the study would have been accounted for in the analysis, (3) participants were analysed in the groups they were randomized to, (4) blinded outcome assessment was used, (5) power calculation information was provided, (6) baseline characteristics of study groups were balanced at the start of the study, and, in case were there was imbalance, adjustment for the imbalance was done in the analyses (see Table 3.3).

Table 3.3: Randomised clinical trials quality assessment checklist

Assessment criteria	**Studies fulfilling criteria**	**Studies not fulling criteria**
Randomization of participants is reported		
All participants who entered the study would have been accounted for in the analysis		
Participants were analysed in the groups they were randomized to		
Blinded outcome assessment was used		
Power calculation information was provided		
Baseline characteristics of study groups were balanced or adjustment for the imbalance in analyses		

Observational studies with a control group were assessed to see whether (1) participants, both groups, were stratified for the cervical cancer prevention or screening method under review, (2) if groups were not stratified for prevention and screening methods and the distribution was unbalanced, we will assess whether the outcomes were adjusted for (see Table 3.4).

Table 3.4: Observational studies with a control group quality assessment checklist

Assessment criteria	Studies fulfilling criteria	Studies not fulling criteria	Studies not applicable
Assessment of participants' on admission to study			
Assessment of treatment method under review			
Participants were stratified for the cervical cancer treatment method under review			
Ascertainment of cervical cancer and HIV status, prospectively from participants through diagnosis, laboratory tests and blood tests			
Ascertainment of cervical cancer and HIV status, retrospectively from participants through diagnosis, laboratory tests and blood tests			
Complete follow up - all subjects accounted for			
Subjects lost to follow up unlikely to introduce bias (≥75% follow-up or description provided of those lost			
If groups were not stratified for treatment methods and the distribution was unbalanced, were outcomes adjusted for			

For observational studies without a control group, we assessed whether (1) the study population was a consecutive cohort of participants, (2) included participants have fulfilled predefined criteria, (3) study design (prospective or retrospective) information was given (see Table 3.5).

Table 3.5: Observational studies without a control group quality assessment checklist

Assessment criteria	Studies fulfilling criteria	Studies not fulling criteria
Study population was a consecutive cohort of participants		
Included participants have fulfilled predefined criteria		
Study design information given.		

For the outcome measures in all study groups, we assessed whether (1) a predefined outcome measure was defined and (2) any method or cervical cancer prevention or screening was used or information on its application was given (see Table 3.6).

Table 3.6: Outcome measures' quality assessment checklist

Cervical cancer prevention methods	Assessment criteria	Studies fulfilling criteria	Studies not fulling criteria
Pap smear	Clinical definition		
	Technical investigation		
	Definition of results		
VIA	Clinical definition		
	Technical investigation		
	Definition of results		
HPV DNA	Clinical definition		
	Technical investigation		
	Definition of results		
HPV vaccination	Clinical definition		
	Technical investigation		
	Definition of results		

Screening of search results, quality examination and extraction of relevant data, was carried out by two independently working researchers. Any discrepancies and disagreements that arose during the review study were resolved through discussion. The average of the two reviewers was the quality score for each study, where a range of zero (lowest quality) to five (highest quality) was used. Studies were not excluded based on quality rating but quality results which were included in the synthesis of the findings.

3.3 Protocol for the systematic review on treatment of cervical cancer in HIV seropositive women from developing countries

The PRISMA-P statement (see Appendix 6) guided the development and reporting of this protocol whilst the systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[76] and registered with PROSPERO database (CRD42018095707)[77].

3.3.1 Studies' eligibility criteria

Studies were included if

- Cervical cancer treatment methods for HIV positive women (such as chemotherapy, radiation therapy, surgery, cryotherapy and targeted therapy among others)
- Cervical cancer treatment methods and HIV are considered being independent and outcome variables
- Published in peer-reviewed journals and grey literature (conferences, dissertations, government health reports)
- They were done in or for countries or regions that are considered developing by the United Nations[78]
- They are observational study designs (retrospective cohorts, prospective cohorts, cross-sectional and case-control) or randomised controlled trials

Studies done across developed and developing countries, the team followed the same guidance as the methodology around the prevention systematic review. The review team extracted results from the developing countries where it was possible and contacted study authors for more information if the information was not available.

Studies were excluded if they were describing cervical cancer in general, their samples were unrepresentative (non-parametric tests as alluded to in the previous protocol, were used to determine unrepresentative samples) or if they were reviews. No studies were excluded

because of the length of the follow up period; instead, follow up periods were used to assess the quality of the study outcomes. Non-English language studies, reports and dissertations were also sought as part of the search strategy and translation of data was performed by a volunteer where feasible.

3.3.2 Search strategy

Two independently working reviewers (WM and BGB) searched MEDLINE (1966–present) and Embase (1980–present) via the OVID interface, PubMed, Cochrane and CINAHL (1961–present) using a combination of the following words: cervical cancer, treatment, developing countries, HIV, chemotherapy, radiation and surgery (see Table 3.7 and Appendix 7). In addition, the two reviewers (WM and BGB) also searched the 3ie Systematic Reviews, WHO library and databases, World Bank website and WHO ICTRP and cliniccaltrials.gov. Proximity operators, Boolean logic operators and truncation commands (see Table 3.2) were used as suggested. To search for additional and relevant papers, reference and citation tracking were conducted.

Table 3.7: Medline and Embase search strategy via OVID interface

Search Terms	
1.	Cervi* canc*.mp. [mp=title, abstract, full text, caption text]
2.	cervi* neoplas*.mp. [mp=title, abstract, full text, caption text]
3.	cervi* carcinom*.mp. [mp=title, abstract, full text, caption text]
4.	cervi* dysplas*.mp. [mp=title, abstract, full text, caption text]
5.	cervi* intraepithelial neoplas*.mp. [mp=title, abstract, full text, caption text]
6.	treat* or therap*.mp. [mp=title, abstract, full text, caption text]
7.	chemotherap* .mp. [mp=title, abstract, full text, caption text]
8.	surger*.mp. [mp=title, abstract, full text, caption text]
9.	radiation adj3 therap*.mp. [mp=title, abstract, full text, caption text]
10.	cryotherap*.mp. [mp=title, abstract, full text, caption text]
11.	HIV positive.mp. [mp=title, abstract, full text, caption text]
12.	hiv seropositiv*.mp. [mp=title, abstract, full text, caption text]
13.	hiv.mp. [mp=title, abstract, full text, caption text]
14.	developing countr*.mp. [mp=title, abstract, full text, caption text]
15.	underdeveloped countr*.mp. [mp=title, abstract, full text, caption text]
16.	low income countr*.mp. [mp=title, abstract, full text, caption text]
17.	low resource countr*.mp. [mp=title, abstract, full text, caption text]
18.	low resource setting*.mp. [mp=title, abstract, full text, caption text]
19.	developing countries.mp. [mp=title, abstract, full text, caption text]
20.	1 or 2 or 3 or 4 or 5
21.	6 or 7 or 8 or 9 or 10
22.	11 or 12 or 13
23.	14 or 15 or 16 or 17 or 18 or 19
24.	20 and 21 and 22 and 23

3.3.3 Study selection

The search of databases and grey literature yielded 1514 results and an additional four studies were identified through reference tracking to make 1518 articles. All the articles (1518) were combined into EndNote reference management software and 229 duplicates were removed. The remaining 1289 articles were exported to Covidence software, were duplicate screening was performed. Two independently working reviewers (WM and SF) conducted title and abstracts screening based on the relevance to the review question. Studies were excluded when title and abstract mentioned cervical cancer screening or vaccination or described implementation process of a cervical cancer treatment. Disagreements related to the screening process were resolved as a team through discussions. Through title and abstract screening, 1106 articles were excluded. Two independent reviewers (WM and BGB) conducted full text

screening (see Appendix 8) on the remaining 183 articles and 171 articles did not meet the eligibility criteria and were excluded. A total of 12 articles met the eligibility criteria and included in the final analysis.

3.3.4 Data extraction

Two independent reviewers (WM and TC) conducted double data extraction in Covidence software on the 12 articles that were included in the final analysis, whilst the rest of the team checked for quality and consistency. A data extraction form (see Appendix 9) guided data extraction. The team discussed and resolved all the inconsistencies through consensus. The following variables were extracted from the studies: first author and publication year, title of the study, study type, aim of the study, participants and their age, study setting, stage of cervical cancer, treatment method, outcomes, results and authors' conclusions.

3.3.5 Quality assessment

The team utilised a combination of the NIH Study Quality Assessment Tools for observational and cohort cross-sectional case control and before-after studies[82] and a modified version of the Newcastle-Ottawa Quality Assessment Scale[81] for quality assessment of the studies. Two independent reviewers (WM and SF) conducted the quality assessment and no studies were excluded based on quality. Answers to the questions of the two checklists gave an overall score of each article. An average of the scores from the two reviewers became the final quality score for each study. Quality was bench marked as low, moderate, and high.

Randomised controlled trials were assessed according to the criteria in Table 3.3, whilst observational studies with a control group were assessed according to Table 3.4, observational studies without control groups assessed according to Table 3.5 and the quality of the studies' outcomes assessed according to Table 3.6.

3.4 Methodology of the cross-sectional survey

This methods section describes the cross-sectional research design study used to investigate the knowledge, attitude and practices of young people in Zimbabwe toward cervical cancer, its risk factors, screening and HPV vaccination. The section also describes the study population and participants, sampling procedure, sample size, measures and procedure used for data collection and the method of data analysis.

3.4.1 Study design

The study is a cross-sectional survey design. A cross-sectional survey design was selected because the researcher was investigating the knowledge, attitude and practices of young people in Zimbabwe toward cervical cancer, risk factors, screening and HPV vaccination.

3.4.2 Location of participants and sampling design

The study participants were recruited from six high schools and five universities in five of the ten provinces in Zimbabwe. Two separate samples, high school and university students, were chosen differently. Three-stage cluster sampling was used to select study participants (see Figure 3.1). Zimbabwe's ten provinces were used as the sampling units for the first stage. The ten provinces were written on separate paper sheets and these were put in a box where a lottery method was used to select five provinces. The districts of the selected five provinces were used as the sampling units for the second stage. The same process was used. All the districts in each of the selected five provinces were placed in a box for lottery selection of one district per previously selected province. Universities in each of the five selected provinces, and high schools within the five selected districts, comprised the third stage of sampling. High schools participants who provided consent were recruited for the study through a modified systematic random sampling of every fifth student. High school class lists were used as sampling frames. There was automatic inclusion in the study for the universities within the five selected provinces. If a selected province had more than one university, random selection of one

university among the total was carried out (see Figure 3.1). Purposive sampling was used to select university participants. This was because it was difficult and challenging in terms of the logistics to disrupt lectures to have all the potential participants in a central place. Sex was not considered as a selection criteria for either high school or university participants.

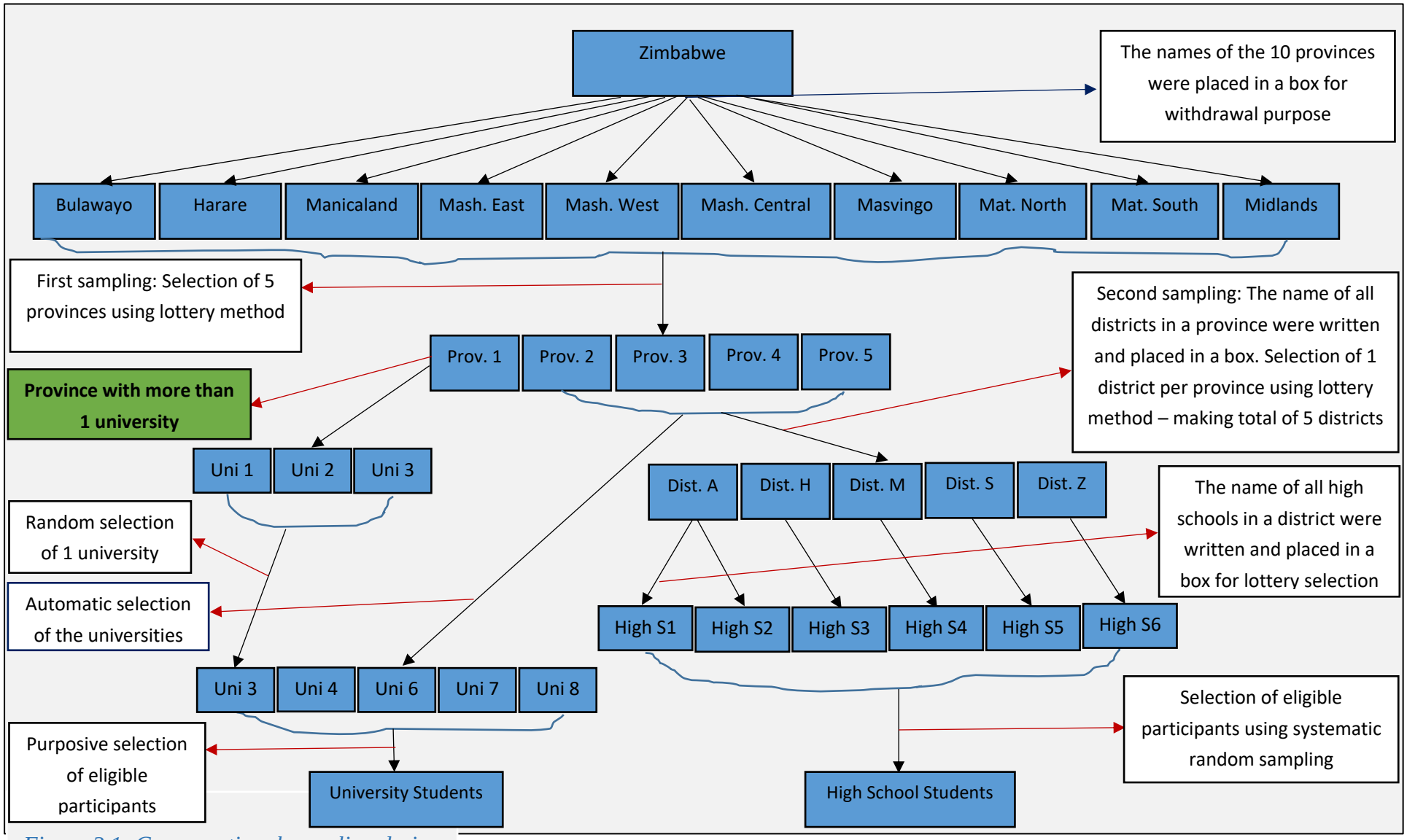

Figure 3.1: Cross-sectional sampling design

3.4.3 Sample size

There was a large population that fitted the demographic inclusion criteria for this research. The 2012 national census was used to calculate the population proportion of the two groups (15-19 years old and 20-24 years old) and respective sample sizes for this research. According to the 2012 national census (see Table 3.8), the total Zimbabwean population was estimated to be 13 061 239 and there were 1 412 033 individuals aged 15-19 years old and 1 195 664 aged 20-24 years old. Therefore, the population proportion for the two respective groups were:

Table 3.8: Zimbabwe 2012 census data

Provinces/Age groups (years)	Males	Females	Totals	Total Zimbabwean Population
Bulawayo				
15 – 19	33923	44282	78205	
20 – 24	31803	41436	73239	
Manicaland				
15 – 19	97318	92033	189351	
20 – 24	64166	78338	142504	
Mashonaland Central				
15 – 19	62544	56879	119423	
20 – 24	48950	53125	102075	
Mashonaland East				
15 – 19	74785	67662	142447	
20 – 24	53895	59998	113893	
Mashonaland West				
15 – 19	81121	78315	159436	
20 – 24	69100	73847	142947	
Matabeleland North				
15 – 19	43156	39911	83067	
20 – 24	29180	33426	62606	
Matabeleland South				
15 – 19	42508	38585	81093	
20 – 24	26640	30181	56821	
Midlands				
15 – 19	90276	88871	179147	
20 – 24	66011	78962	144973	
Masvingo				
15 – 19	79740	80226	159966	
20 – 24	45939	65199	111138	
Harare				
15 – 19	93859	126039	219898	
20 – 24	107782	137686	245468	
Totals				
Total 15-19	699230	712803	1412033	
Total 20-24	543466	652198	1195664	
Totals	1242696	1365001	2607697	**13061239**
Proportions by age groups				
15 – 19			11%	
20 – 24			9%	
Proportions by sex and age group				
Male 15-19			50%	
Female 15-19			50%	
Male 20-24			45%	
Female 20-24			55%	

For the 15-19 age group = 1412033/13061239 = 11%.

For the 20-24 age group = 1195664/13061239 = 9%.

Power analysis was conducted assuming power of .80 and an alpha of .05. An average response rate of 85% was factored-in to adjust for sample sizes. A design effect of 3 was also factored-in as an adjustment to the survey sample size, due to the cluster sampling that was involved**.**

Therefore, using the formula; $\mathbf{n = (z/p)^2 \pi (1-\pi)}$

Where n = the required sample size

p = the desired maximum discrepancy (±5)

π = population proportion

z = z value at 95% CI from the Normal distribution (1.96)

For the 15-19 age group

$n = (1.96/0.05)^2\ 0.11(1-0.11)$

$n = 150.437$

Adjusting for response rate which is 85%,

$n = 150.437/0.85$

$n = 176.985$

$n = 177$

Adjusting for the design effect, $177*3 = \underline{531}$

Therefore, the minimum sample size for the 15-19 age-group, was **531** participants.

For the 20-24 age group

$n = (1.96/0.05)^2\ 0.09(1-0.09)$

n = 125.85

Adjusting for response rate which is 85%,

n = 125.85/0.85

n = 148.059

n = 149

Adjusting for the design effect, 149*3 = 447

Therefore, the minimum sample size for the 20-24 age-group was **447** participants.

3.4.4 Ethical aspects

The researcher and his two research assistants received three days of training. The training covered, among others, study information giving and informed consent process, administration of the questionnaire and general data management processes. Ethical permission (see Appendix 18) to conduct the study was obtained from the Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria and ministries of Health and Child Care, Primary and Secondary Education, and Higher and Tertiary Education in Zimbabwe. The Medical Research Council of Zimbabwe provided ethical clearance and permission to access high schools and universities was sought from the Provincial Educational Officers, high school principals as well as university Vice-Chancellors.

Participants were both verbally informed and provided with written information that enrolment for the study was voluntary and that they could withdrew from the study at any time without any consequences to their studies, health or social life. The aims of the study were explained to the participants verbally as per the information sheet (see Appendix 10). Written informed consent was required from each study participant and the participant was given a copy of their written consent as record. Consent forms (see Appendix 11) were translated into Zimbabwe's

local languages, Shona and Ndebele, as necessary. Names of participants, their home addresses or phone numbers are not in any reports arising from this study.

Since the study involved no more than minimal risk, permission of one parent (see Appendix 12) was sufficient for the under 18 years' children to assent or dissent (see Appendix 13) to participating. Participation in the research was presented as a voluntary choice and no pressure or coercion was applied to the children to encourage participation. This information was made available to the children for them to comprehend and appreciate that they were volunteering to participate for the likely benefit of others. The information giving process was age-appropriate and suitable for the children's cognitive and emotional maturity. Dissent was honoured and respected even when a parent had consented because the decision to participate in the study lay with the child.

The study collected sensitive information such as drinking and smoking history, which likely presented risks to the children. Furthermore, in a closed environment like a school, there was likelihood of sensitive information being amplified if confidentiality was not maintained. Special precautions in recruiting the children, data collection, information on data storage and publications was taken to protect the privacy of the participating children.

3.4.5 Study instrument, data collection and data management

The questionnaire's questions were based and adapted from the concepts of the HBM and the Cervical Cancer Measuring tool kit-UK. The content validity of the questionnaire was established by giving the items to experts to assess the relevance of the questionnaire in line with the study objectives. After validation, the questionnaire was pilot-tested on 40 conveniently selected young people aged between 15 to 24 years.

Data were collected from August to November 2017 at the high schools and universities after approval from all relevant institutes and ministries. The self-administered questionnaire

covered a range of issues including; (1) demographics, (2) cervical cancer knowledge, (3) cervical cancer risk factors, (4) HPV knowledge, (5) cervical cancer screening and vaccination (see Appendix 14). The self-administered survey could take 30 minutes or less to complete. To guard against their privacy, respondents sat at desks in a provided classroom and were invigilated by the researcher or research assistants. After respondents completed the questionnaire, they handed it to the researcher or research assistants who reviewed it for completeness. Respondents with incomplete questionnaires were given an opportunity to answer and complete the questionnaire. At all levels of data collection, there was continuous checking of data quality. Collected questionnaires were placed in secure boxes and transported to a central office in Harare. Data were kept under lock and key at the office.

Data entry and coding were done centrally and independently by the researcher in consultation with the research assistants. Entry coding of data using EpiData Software Version 4.2 and Microsoft Excel and verification, were a continuous process and issues arising were discussed with research assistants and followed up to ensure no delays or missing data. Missing values within the dataset were found by using frequency and summary tables. Checks for inconsistencies were carried out. Data were checked against questionnaires and any changes to the data were documented and stored separately from the main database. A file for data cleaning was created. Any missing data were documented and sensitivity analysis carried out to compare results from complete case analysis. Records with missing data were removed. All survey questionnaires have been submitted to the Faculty of Health Sciences, University of Pretoria, for storage for 15 years as per the University's policy.

3.4.6 Data analysis

Data were analysed using Stata Software Version 14.0. Response rate and descriptive statistics such as proportion of male to female, and percentages, were used in summarising categorical characteristics of participants.

Descriptive statistics for the study samples were calculated without any adjustment for the complex sample design since the aim was simply to describe the samples. However, for analytical hypothesis testing and regression modelling the clustering inherent in the study design was taken into account using Stata's survey ("svy") module.

The profile of the respondents was used to identify certain shared or divergent traits. To assess knowledge on cervical cancer, cervical cancer risk factors, cervical cancer screening and HPV vaccination, frequencies and percentages were used to express the results. Cronbach's alpha was used to measure internal consistency of the Likert questions used to form construct variables. To determine the factors associated with knowledge of cervical cancer, its risk factors, screening and HPV vaccination, logistic regression models were used. Variables with a p-value of 0.25 or under in univariate analyses were unconditionally included in the initial saturated backward stepwise regression model[83]. Following stepwise hierarchical backwards regression modelling, explanatory variables were only removed from the models if the results of an LR test yielded a p-value of greater than 0.2[83]. Results of the association were expressed as adjusted odds ratios with 95% confidence intervals. Post-regression tests were carried out to assess the goodness of fit of the regression model as well as the area under the roc curve[83]. Relationship of association between knowledge and attitude was determined using Chi-squared tests. Significance was assumed at two-sided value of $p < 0.05$.

To each participant of the selected high school sample, a weight equal to the inverse of the probability of selection was calculated and taken into consideration to obtain estimates of population parameters. The weighting process accounted for the sample selection, important since the initial probabilities of selection were not influenced by population sizes of the sampling units (see Table 3.9). The weight adjustments coincided with known totals of the high schools, districts and province populations.

When estimating population parameters, including those obtained from logistic regression, estimates were obtained following use of Stata's "svy set" command and the use of the "svy:" prefix for commands, as mentioned above (for example: *svy: logistic ccknowledge age gender i.province i.residence*); so that the sampling structure can be taken into consideration when estimating variances as well as confidence intervals and p-values.

Table 3.9: Weights of high school sample

school_name	district_name	province_name		P	w = 1/p
School 1	District 1	Manicaland	(5/10)*(1/8)*(1/11)*(42/261)	0,000914	1093,7143
School 2	District 2	Mashonaland West	(5/10)*(1/8)*(1/12)*(42/260)	0,000841	1188,5714
School 3	District 3	Masvingo	(5/10)*(1/7)*(1/14)*(45/272)	0,000844	1184,7111
School 4	District 4	Midlands	(5/10)*(1/8)*(1/10)*(39/244)	0,000999	1001,0256
School 5	District 5	Harare	(5/10)*(1/1)*(2/31)*(32/225)	0,004588	217,96875
School 6	District 5	Harare	(5/10)*(1/1)*(2/31)*(38/240)	0,005108	195,78947

3.5 Chapter three summary

The proposed study was an integrative approach of two systematic reviews and a cross-sectional survey. The purpose of the two systematic reviews was to explore the available screening/prevention and treatment modalities for cervical cancer for HIV-positive women in developing countries. The purpose of the cross-sectional survey was to assess the knowledge, attitudes and practices of young people in Zimbabwe towards cervical cancer, its risk factors, screening and HPV. In distinguishing between the two systematic reviews and the cross-sectional methods, my purpose was to provide a map of how each of the components was carried out. Articles that were utilised for the systematic reviews were identified through searching the following databases: MEDLINE, Embase, PubMed, CINAHL, Cochrane Library, health databases which cover developing countries (3ie Systematic Reviews, WHO library and databases, World Bank website) and databases containing on-going research (such as WHO ICTRP and clinicaltrials.gov). Young people were recruited from high schools and universities in Zimbabwe. Two separate samples were selected through a three-staged cluster sampling method that utilised provinces, districts, and schools/universities. Ethics clearance for the

study was sought and granted by: the Faculty of Health Sciences Ethics Committee, University of Pretoria; Medical Research Council of Zimbabwe; Ministries of Health and Child Care; Primary and Secondary Education; and Higher and Tertiary Education of Zimbabwe. Written consent was sought and collected before each participant was given the questionnaire to complete. The researcher and his research assistants checked for completeness of the questionnaires and maintained quality throughout the data collection process. EndNote, Covidence, EpiData and Microsoft Excel, were used for data management. The laid out methodology helped out with the evidence syntheses, collection of data and analysis and chapter four provides the results of this research.

CHAPTER FOUR: RESULTS

Note: Some of the presented results in this chapter have been published in BMC Systematic Reviews Journal (see Appendix 19).

4.1 Introduction

This chapter presents the main findings of the two systematic reviews and the cross-sectional survey. The purpose of this chapter is to provide results from the synthesised and documented published evidence relating to the available cervical cancer prevention and treatment modalities for HIV-seropositive women in developing countries; and the survey on knowledge, attitudes and practices of young people (15 to 24 years old) in Zimbabwe towards cervical cancer, screening, HPV and vaccination. This chapter results are structured as follows:

- Section 4.2 presents synthesised evidence on cervical cancer screening strategies currently used for HIV-seropositive women in developing countries,
- Section 4.3 presents synthesised evidence on treatment modalities available for HIV-seropositive women with cervical cancer in developing countries and finally
- Section 4.4 presents results of the cross-sectional survey on the knowledge, attitudes and practices of young people in Zimbabwe towards cervical cancer, its risk factors, screening and HPV vaccination.

4.2 Cervical cancer screening strategies currently used for HIV-seropositive women in developing countries: results of a systematic review

4.2.1 Description of the included studies

Out of 2559 articles, 25 met the inclusion criteria and were synthesised for results (see Figure 4.1). The table of evidence (see Appendix 15) summarises the study characteristics and evidence extracted from the studies respectively. Twenty-two studies (88.0%) were conducted in and for sub-Saharan Africa, two (8.0%) in Asia and one (4.0%) in South America (see Figure 4.2). All the included studies were published within the last decade, 2008 to 2018.

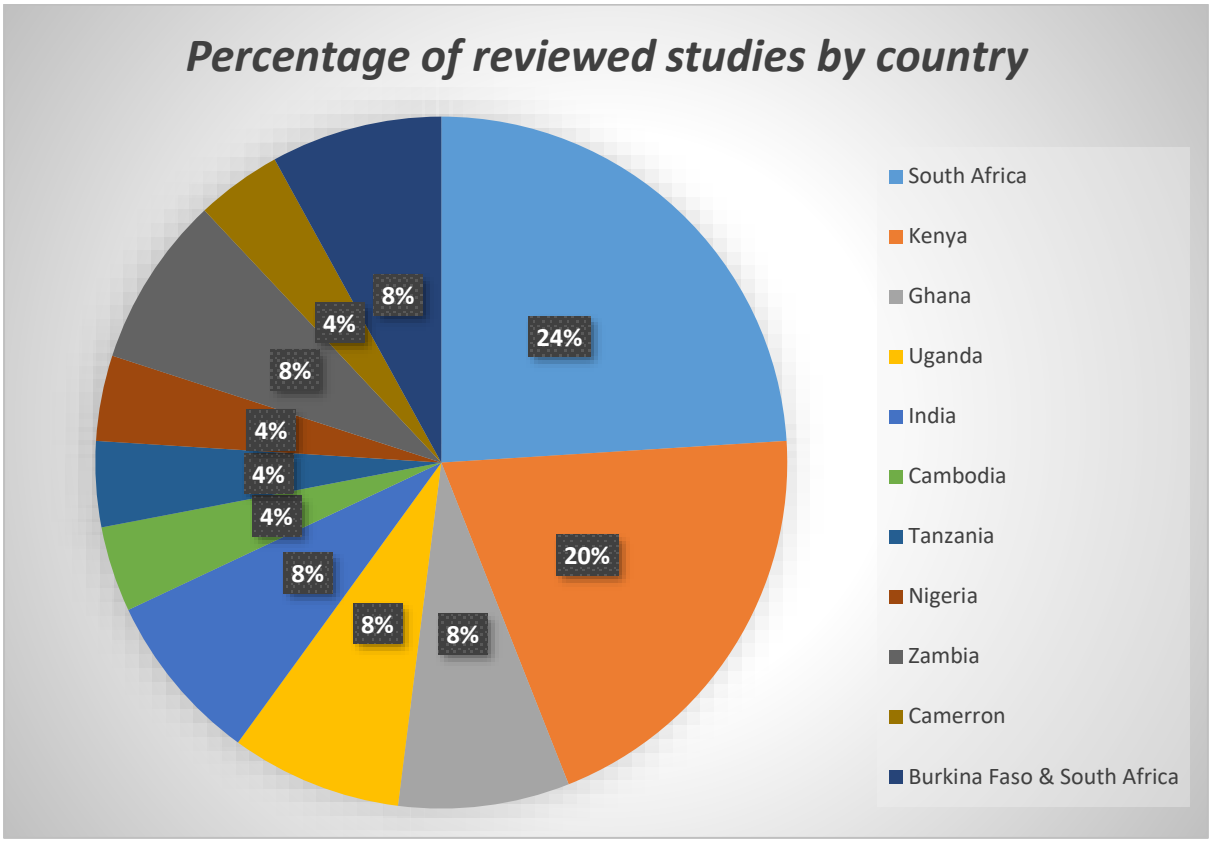

Figure 4.2: Research of cervical cancer screening among HIV-seropositive women by country

All the included studies explored the clinical performance of cervical cancer screening methods/tools on HIV-seropositive women, with a few comparing them to screening HIV-negative women. There was almost complete consistence in defining the key outcomes across the studies to indicate clinical performance, which is, looking at sensitivity, specificity, positive

and negative predictive values. However, the baseline characteristics of the study participants including age varied across the studies. In addition, sampling and recruitment of participants, screening process (opportunistic vs. organised), the interval on which follow-ups were conducted, and the type of visits (one-visit schemes vs. return visit scheme) were also different. Completeness of data, data management methods, adjustment for confounders and analysis also differed across the studies. Therefore, because of this heterogeneity, a narrative descriptive synthesis was performed.

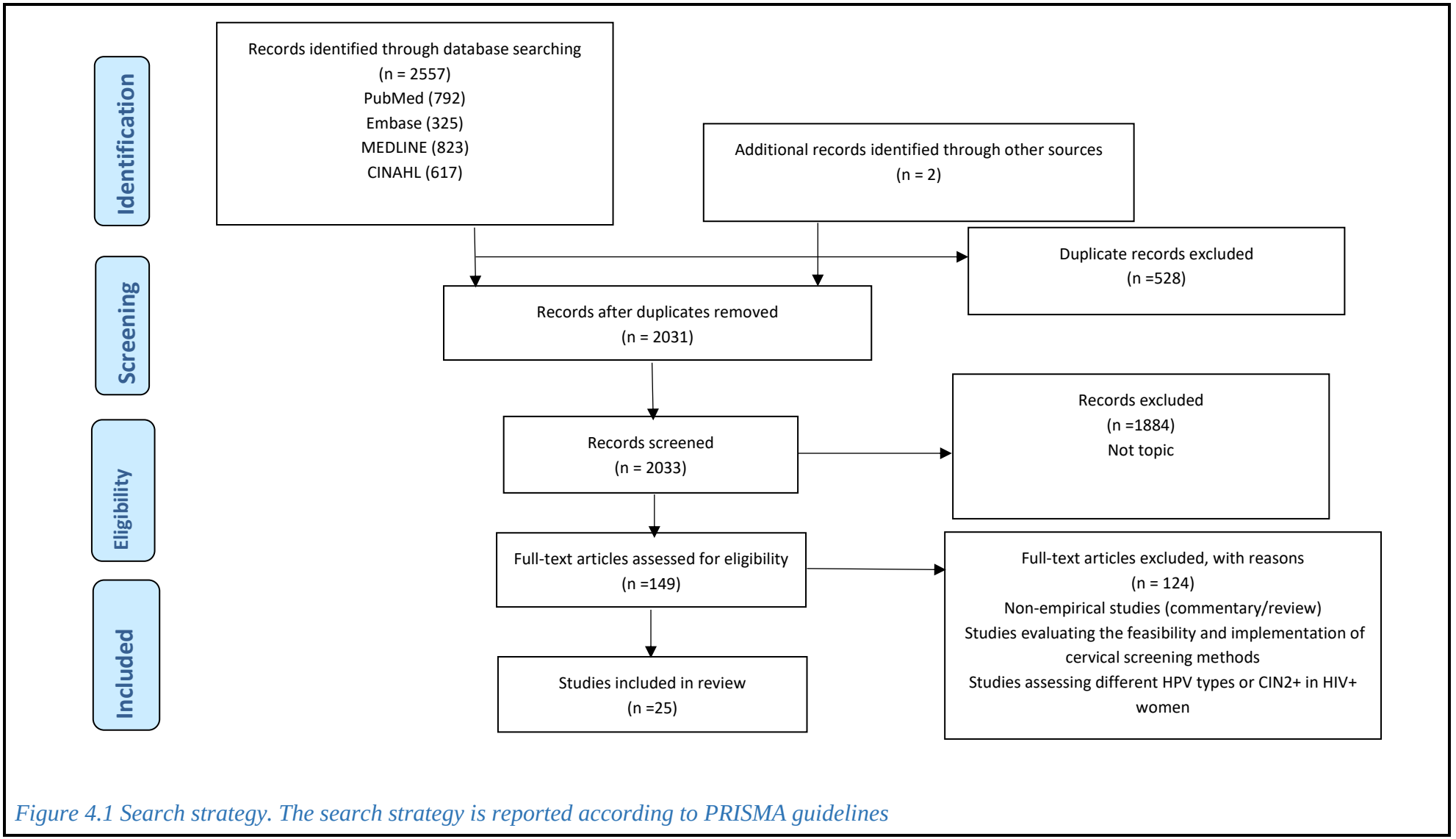

Figure 4.1 Search strategy. The search strategy is reported according to PRISMA guidelines

4.2.2 Study designs of the included studies

The included studies ranged from cross-sectional to randomised clinical trials. Classifying them according to the protocol[84], most of the included studies were observational studies without control groups (n=20, 80.0%). There were three observational studies with a control group (12.0%) and two (8.0%) randomised clinical trials (see Appendix 15).

Of the two randomised clinical trials (see Appendix 15), one compared the diagnostic accuracy between VIA and VILI[85], while the other clinical trial evaluated the efficacy and safety of the screen-and-treat using either HPV DNA test or VIA[86]. The three observational studies with a control group compared VIA to the sequential use of VIA and VILI[87] and the other two assessed the performance of careHPV(®), a rapid batch diagnostic test for detection of high-risk HPV DNA, versus HPV genotyping[88-89].

The twenty observational studies without a control group evaluated clinical performance of VIA, careHPV(®), VILI with digital cervicography, Pap smear, HPV test, HPV DNA, cryotherapy, and Cellslide(®) automated liquid-based cytology[90-102]. The other studies evaluated the see-see and treat strategy of VIA/VILI and cryotherapy[103], Hybrid Capture-2(®) (HC2), INNO-LiPA(®), p16INK4a ELISA(®), Xpert HPV(®), high risk HPV messenger-RNA, and OncoE6(®) for HPV detection[104-109].

4.2.3 Cervical cancer screening methods/tools for HIV-seropositive women

Most of the studies were conducted in sub-Saharan Africa and they evaluated and compared performance of VIA; detecting high-risk HPV DNA using careHPV(®) or INNO-LiPA(®) or HC2(®) or Xpert HPV or OncoE6(®); a combination of VIA/VILI with digital cervicography; Pap smear; colposcopy and test and treat using VIA/VILI or HPV DNA and cryotherapy[85-94,97-109]. The two studies conducted in Asia evaluated VIA, VILI, cytology, HPV testing and colposcopy to find an accurate, feasible and affordable cervical screening method for HIV-

infected women[95,99]. In Cambodia, they compared VIA and Pap smear, looking at the correlation between the two among HIV-infected women[96].

4.2.4 Primary prevention methods

The p16INK4a ELISA(®), a surrogate maker for high-risk HPV, was assessed as a potential primary cervical cancer screening tool for HIV-seropositive women in Kenya[106].

4.2.5 Secondary prevention methods

For secondary prevention, VIA was the most frequently used and evaluated screening method for HIV-seropositive women in sixteen of the twenty-five articles included (n=16, 64.0%). Comparison between Pap smear and VIA to assess which is the better screening method was explored in four of the included articles (n=4, 16.0%). Evaluation of Pap smear, VIA, HPV test and colposcopy was also examined in four of the studies (n=4, 16.0%), whilst VIA and VILI were assessed in only one study (n=1, 4.0%). HPV DNA/mRNA testing with various methods and tools such as HC2(®), INNO_LiPA(®), HPV Genotyping, careHPV(®), hrHPV mRNA, Xpert HPV(®) and OncoE6(®), was evaluated in nine studies (n=9, 36.0%). In the test/screen and treat initiatives, HPV DNA and cryotherapy, VIA and cryotherapy, and VIA/VILI and cryotherapy, were evaluated in two of the studies (n=2, 8.0%).

4.2.6 Efficacy and accuracy of cervical cancer screening methods in HIV-positive women

VIA

A number of studies[86-87,90,92-95,97,99-100,108] have all reported VIA performance in detecting cervical intraepithelial neoplasia grade 2+ (CIN2+) that is generally consistent, with sensitivity of between 55.0%-80.0% and specificity of 65.0%-83.0% (see Appendix 16). However, some evidence[90,97] reported specificity of 47.3% and 51.0%, which are lower than what was found in other studies; while in Zambia[108], there was a reported of a specificity of 92.0%, which was higher than in other areas. As a diagnostic test, VIA had positive and negative predictive values

of 38.6% (95% CI = 28.8%-49.3%) and 79.1% (95% CI = 67.8%-87.2%) respectively[97] and this was comparable to the reported positive predictive value of 35.2%[87].

VILI

Using the CIN2+ threshold (see Appendix 16), VILI has a better sensitivity and specificity when compared to VIA, with sensitivity ranging from 68.0% to 96% and specificity of 71.0% to 91.0%[87,94].

Digital cervicography

Two studies in Zambia reported different efficacy of digital cervicography (DC) in screening for CIN2+ among HIV-positive women. The first study[108] reported a sensitivity of 59.0% (95% CI 41.0-76.0), specificity of 88.0% (82.0-93.0), PPV of 49.0% (32.0-65.0) and NPV of 92.0% (95% CI 87.0-96.0). Whilst the second study[102] indicated that DC had high sensitivity of 84.0% (95% CI 72.0-91.0) but low specificity of 58.0% (95% CI 52.0-64.0), PPV of 33.0% (95% CI 26.0-41.0) and NPV of 93.0% (95% CI 88.0-96.0).

Cytology based tests

Sensitivity and specificity of Pap smear in detecting CIN2+ in HIV-seropositive women have been shown to be between 45.0%-76.0% and 58.0%-98.0% respectively[92,95,97,99-100,102]. This clinical performance of Pap smear was similar to Cellslide(®) automated liquid-based cytology which recorded sensitivity of 76.0% (95% CI 64.8-85.1) and specificity of 91.0% (95% CI 87.0-94.2)[98].

Tests/tools for high-risk HPV DNA detection

Sensitivity of HR-HPV DNA detection tests/tools such as careHPV(®), HC2(®) test, INNO-LiPA(®), Xpert HPV(®) and P16INK4a(®) is better when compared to cytology-based tests

and visual tests as indicated by a sensitivity of 80.0%-97%. However, specificity of these HPV tests is similar in some cases but mostly lower to cytology or visual tests, 51.0%-78.0%[86,88-90,92-95,105,107-108]. Although the OncoE6(®) had a specificity of 99.0% (95% CI 97.0-100), it had low sensitivity of between 16.0%-50.0%[108].

4.2.7 Clinical performance of combined screening methods/tests

VIA and Pap smear; VILI and Pap smear

Sequential testing of HIV-seropositive women with VIA and Pap smear did not result in any significant changes in sensitivity which was 50.0%-72.0% but there was significant change in specificity (97.0%-99.5%) when compared to individual VIA or Pap smear screening[92,95]. The clinical performance of testing with both VILI and Pap smear was almost similar to using VIA and Pap smear, with sensitivity being 55.1% (95% CI 40.2-69.3%) and a slightly increased specificity of 99.6% (95% CI 99.0-99.9%).

VIA and HPV testing; VIA/VILI and HC2(®)

Some findings indicated that a combination of VIA and testing for HPV did not improved sensitivity or specificity when compared to use of individual tests, with clinical performance of the combination being sensitivity of 58.2% (95% CI 48.8-67.0%) and specificity of 83.7% (95% CI 79.4-87.2%)[92]. However, in India, it was reported that the use of either VIA or VILI and HPV testing using HC2(®) showed slightly better performance with sensitivity of 85.5% (95% CI 73.3-93.5%) and specificity of 95.3% (93.9-96.5%)[95].

VIA and VILI

The use of a combination of VIA and VILI in detecting CIN2+ in HIV-seropositive women resulted in increased clinical performance with sensitivity of 81.8% (95% CI 69.1-90.9%) and specificity of 93.2% (95% CI 91.5-94.6%)[95]. These results indicate that a combine use of both

VIA and VILI have can counter false positive results that are prone when both are used as sole methods[103].

Screen-and-treat method

In a follow-up of 36 months, screen-and-treat using HPV DNA testing and cryotherapy significantly reduced CIN2+ in HIV-positive women, with a relative risk of 0.20, 95% CI (0.06-0.69). Screen-and-treat using HPV DNA testing and cryotherapy had better positive outcomes when compared to screen-and-treat using VIA and cryotherapy[86]. In Uganda, findings indicated that using VIA and cryotherapy alone has the potential of resulting in over treatment of patients because of high false positive rates[103]. To reduce these high false positive complications, a see-see and treat method using VIA, colposcopy and cryotherapy was seen to be effective as it reduced overtreatment by 72% (439/625)[103].

4.2.8 Quality assessment of included studies

Overall, most of the studies (n=16, 64.0%) were determined to be of moderate quality, that is a score of 3 ‘yes’ out of 5 on the quality scale. Only four studies (16.0%) were considered ‘high’ quality, that is, a score of 4 ‘yes’ out of 5. Five studies (20.0%) were considered to be of low quality and had a score of 2 ‘yes’ or below out of 5.

Only five studies (20.0%) had control groups and this made it difficult to confidently ascertain if the reported findings were due to the screening method or it was by chance. Most of the studies did not evaluate the value of the screening modalities since they did not follow-up the screened individuals to fully assess their effectiveness or account for disease regression or progression. Although a few studies followed-up the screened HIV-positive women, the follow-up period was not adequate to measure the effectiveness of the screening methods or offer reasons for lost to follow-up of those who were due for their second screening procedure.

Some of the studies did not measure confounders or include them in their analyses, with a few mentioning confounders and their expected influence on the results.

There was limited study design and methodology description in some articles and this made it difficult to gauge if the reported findings were from an evaluative programme instead of a rigorous research. There was no mention of how participants were randomised or if randomisation was conducted in some of the studies that had a control group and this made it difficult to attribute the reported results to the evaluated screening methods. In studies that evaluated a number of screening methods, there is a likelihood that some might have overestimated the sensitivity and specificity of the screening methods because in their analyses they failed to calculate a dichotomous result to cater for those with negative screening results from other methods.

4.3 Cervical cancer treatment strategies currently used for HIV-seropositive women in developing countries: results of a systematic review

4.3.1 Description of included studies

Out of the initial 1289 (after 229 duplicates were removed), 12 studies (of over 2790 patients) met the inclusion criteria and were included to form the basis of the analysis (see Figure 4.3). A summary of the relevant outcomes or evidence from each included article, other relevant variables, and the quality score of the studies are presented in table of evidence (see Appendix 17).

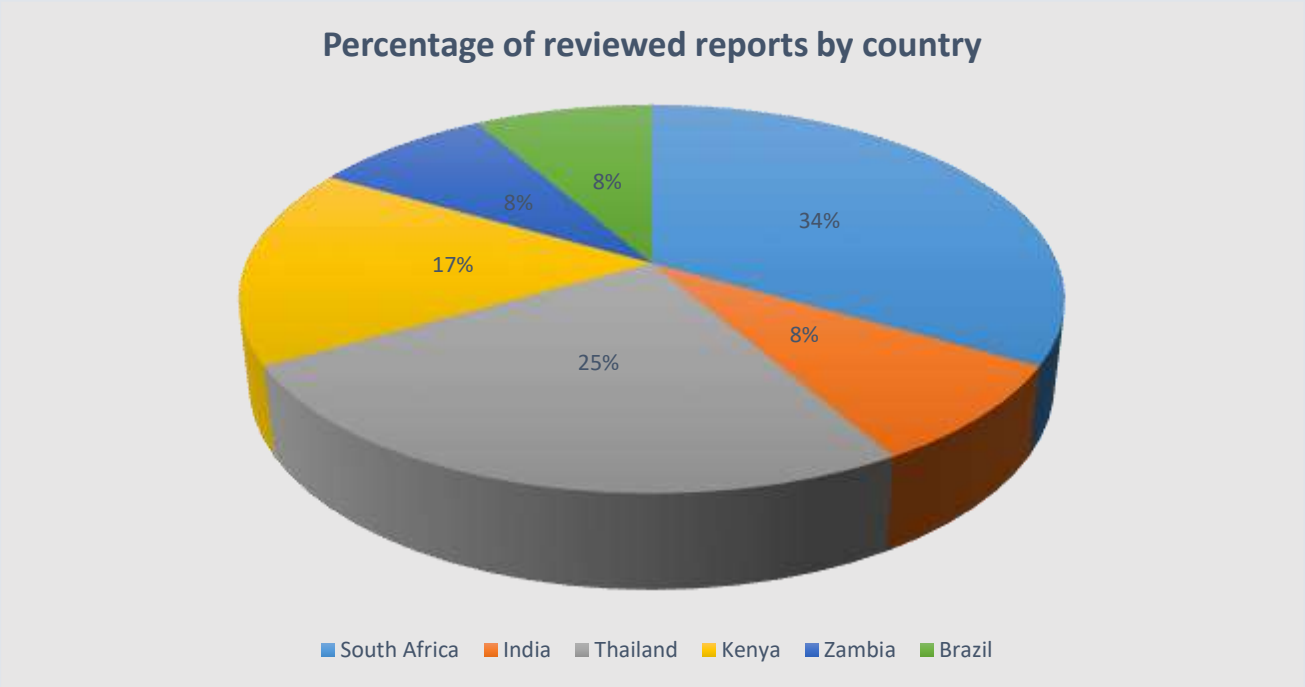

Figure 4.4: Research of cervical cancer treatment among HIV-seropositive women by country

The included studies evaluated, assessed or compared the effectiveness, treatment response and outcomes of different cervical cancer treatment methods for HIV-seropositive women. Most of the studies (66.7%) were published after year 2010. The studies represented three regions, sub-Saharan Africa 7 (58.3%), Asia 4 (33.3%), and South America 1 (8.3%), as indicated in Figure 4.4.

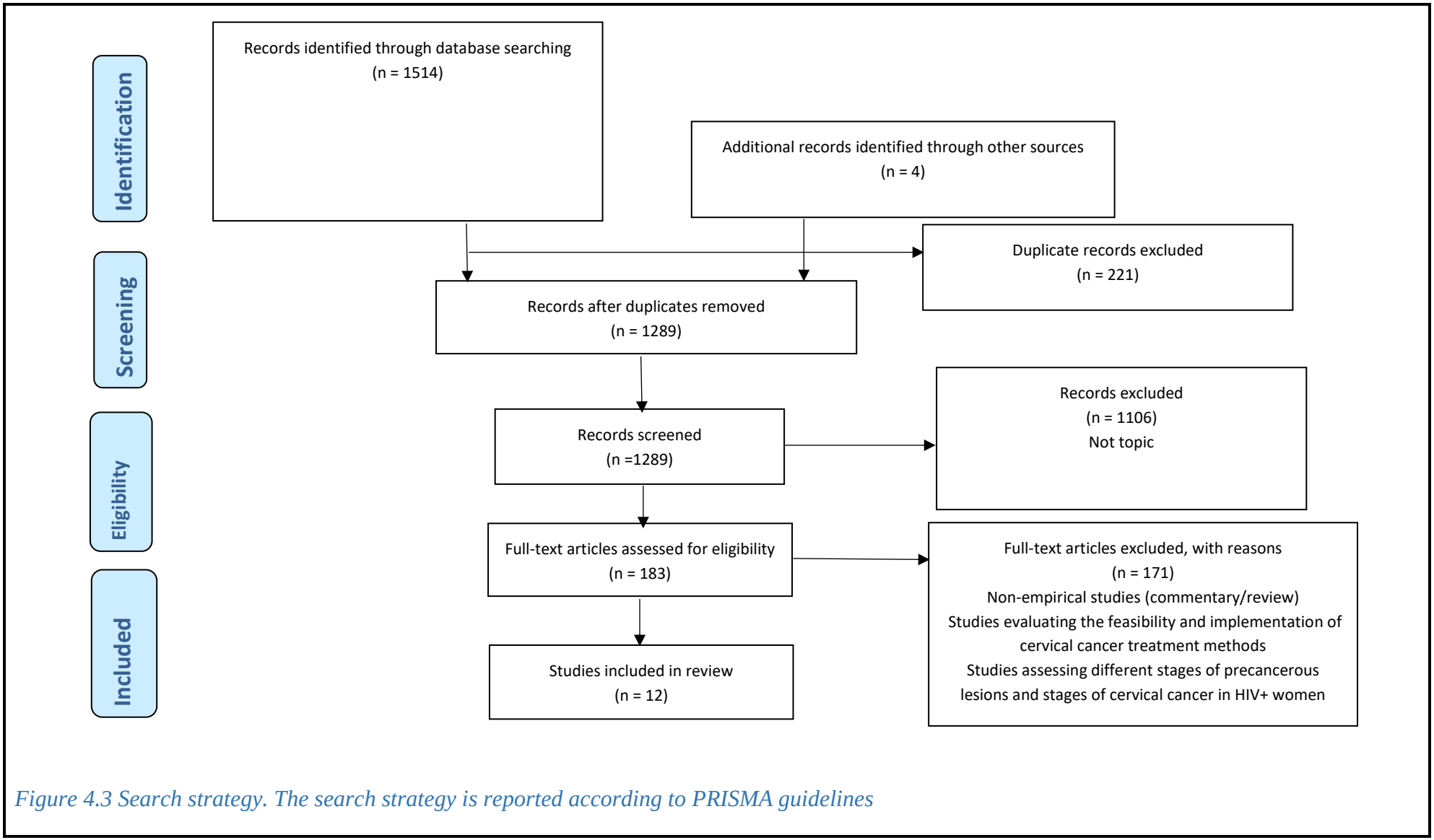

Figure 4.3 Search strategy. The search strategy is reported according to PRISMA guidelines

4.3.2 Study designs of included studies

Five of the included studies (41.7%) are prospective cohort, evaluating treatment response and toxicity to a combination of radiotherapy and chemotherapy, treatment with surgery and radiation, and treatment with loop electrosurgical excision procedure (LEEP). Four (33.3%) retrospective cohort studies evaluated the survival outcomes of chemotherapy, treatment outcomes of radiotherapy and complications with LEEP, and compared clinical characteristics after radiation and chemotherapy. Two (16.7%) randomised controlled trials compared the efficacy of LEEP vs cryotherapy, and cryotherapy with no treatment. One (8.3%) case study examined the results of a radical hysterectomy surgery on two different patients (see Appendix 17). All the 12 studies were almost consistent in defining their outcomes, such as, treatment response, clinical/prognostic characteristics, survival response, and mortality rates. However, baseline characteristics of participants included in the studies were different, with age ranging from 18 years old to well above 55 years old. Sampling and recruitment of the participants was also different. In addition, participants had different stages of both precancerous lesions and cervical cancer, some were on highly active antiretroviral therapy (HAART), whilst others were not on HIV treatment, and the follow-up intervals were different as well.

4.3.3 Treatment options for cervical neoplasia for HIV seropositive women

Five (41.7%) of the 12 included studies evaluated efficacy, treatment outcomes and complications in HIV-seropositive women with cervical neoplasia treated with LEEP or cryotherapy. Three studies evaluated LEEP[110-112]; one compared cryotherapy with no treatment[113], and the other compared LEEP and cryotherapy to identify the effective treatment[114].

LEEP

Three studies reviewing LEEP among HIV-positive women concluded that the procedure is safe and effective. A retrospective cohort study in Thailand evaluated treatment outcomes and complications of HIV-infected and HIV-negative women with low-grade squamous intraepithelial lesion (LSIL) or high-grade squamous intraepithelial lesions (HSIL) undergoing LEEP[111]. The HIV-infected cohort had a mean age of 35.9 years as compared to 40.1 years of the HIV-negative cohort. After 6 and 12 months of LEEP, 97.1% and 88.0% of HIV-infected women had no cervical neoplasia, respectively. In terms of complications, there was no significant difference (p=0.24) when compared to HIV-negative women[111]. These findings were almost similar to evidence generated in the same country two years later, which found out that there was no significant association between HIV and LEEP complications among women with cervical intraepithelial neoplasia (CIN) grade 1, 2, 3, and cervical cancer stage 1A1-1B1[112]. In Kenya, a prospective cohort study also confirmed that LEEP was well tolerated and accepted by HIV-positive women who had CIN 2 and 3, 99.0% of participants reporting 'very mild' symptoms of complications. In addition, women with a higher mean CD4+ count were likely to report symptoms of complications as compared to women with lower mean CD4+ counts[110].

Cryotherapy

In a randomised controlled trial in South Africa among HIV-infected women with CIN1, treatment with cryotherapy was found to significantly reduce progression to CIN2/3. After 12 months, only 2% of women who were undergoing cryotherapy treatment progressed to CIN2/3 as compared to 15% of those who were not receiving treatment who progressed to developing CIN2/3 (86% risk reduction, 95% CI 69%-97%, p=0.0016]. There was regression (decrease in

size/extent of the tumour) was also significant in women receiving cryotherapy as compared to those not receiving treatment (69% reduced regression, 95% CI 58%-83%, p=0.0001)[113].

Cryotherapy vs. LEEP

To try and identify an effective treatment method between cryotherapy and LEEP for high-grade cervical precursors (CIN2+) among HIV-seropositive women, a randomised controlled trial was conducted in South Africa[114]. After 6 months of treatment, there was higher cumulative CIN2+ incidence for cryotherapy (24.3%, 95% CI 16.1-35.8) as compared to LEEP (10.8%, 95% CI 5.7-19.8) at p=0.02. However, after 12 months of treatment, there was no significant difference between the two (27.2%, 95% CI 18.5-38.9 vs. 18.5%, 95% CI 11.6-28.8) at p=0.21[114]. Both cryotherapy and LEEP are effective in reducing CIN2+ and a choice might be based on available resources and expertise.

4.3.4 Treatment options for cervical cancer for HIV seropositive women

Treatment of cervical cancer with radiation, chemotherapy, concurrent treatment using radiotherapy and chemotherapy, and surgery among HIV-seropositive women, was evaluated in 7 (58.3%) out of the 12 included studies. One study compared the clinical characteristics after radiation and chemotherapy among women with cervical cancer IBi-IIB[115], whilst another study evaluated the treatment response of HIV-positive women with IB_2-IIIB cancer to radical combination therapy of radiotherapy and chemotherapy[116]. One study determined the effect of radiotherapy on HIV-positive women and assessed tumor response, toxicity and treatment compliance[117], whilst the other determined HIV-infection's impact on pelvic control and acute morbidity following radiotherapy[118]. Other studies evaluated the survival outcomes of chemotherapy among women with cervical cancer stage IVB[119], mortality and treatment response to surgery, radiation, and chemo-radiation among women with cervical cancer stages

IA/IB1, IB2/II, III, IVA/IVB[120], and radical hysterectomy outcomes on two women with differentiated squamous cell carcinoma (LVSI)[121].

Chemotherapy

A retrospective study in Thailand on 173 HIV-positive and –negative patients (with mean age of 50.9 years) with stage IVB cervical cancer, showed modest efficacy, with overall median survival among all patients of 13.2 months. The only independent prognostic survival outcome was recurrence free interval of less than 12 months[119]. In Brazil, HIV was found not to be associated with mortality due to cervical cancer during the first year post-treatment but association was significant after more than 1 to 2 years post-diagnosis (overall mortality: Adj HR=2.02; 95% CI 1.27-3.22; cancer-specific mortality: 4.35, 1.86-10.2)[120].

Radiotherapy

In a retrospective review conducted in India to determine radiotherapy's effect on HIV-seropositive women of mean age of 41 years with cervical cancer stage IIIB-IVA, indicated that radiotherapy is effective but adherence with treatment is poor (with only 52.4% of women completing the prescribed radical radiotherapy and 50.0% of them achieving complete response)[117]. To overcome poor adherence, palliative radiotherapy schedules were prescribed and these were identified to be effective for HIV-seropositive women with cervical cancer[117]. Despite it being effective, evidence has shown that those undergoing radiotherapy present with acute skin toxicity (grade III), and grade III-IV acute gastrointestinal toxicity[117]. These findings were supported by a prospective cohort study conducted in Kenya, which showed that there was a seven-fold higher risk of developing multisystem (skin, gastrointestinal and genitourinary) toxicity if HIV-infected and following radiotherapy[118]. In addition, this multisystem toxicity has been found as a factor contributing to interruption of treatment (Adj. RR=2.2) [27]. Follow-ups at four and seven months post radiotherapy indicate that HIV-

seropositive are six-fold at risk of having a residual tumour (HR=3.1, p=0.0014) as compared to patients who are HIV-negative[118]. This finding was in accordance with what was suggested in Brazil where there was elevated risk of subsequent relapse for HIV-seropositive women as compared to HIV-negative women (HR=3.60; 95% CI 1.86-6.98)[120].

Radiation and chemotherapy

To compare the clinical characteristics outcomes after radiation and chemotherapy among HIV-positive (median age of 41 years) and –negative women (median age of 50 years) with cancer stage IBi-IIIB, a retrospective cohort study was conducted in South Africa[115]. Treatment completion rates between the two patient cohorts were different, with 79.7% of HIV-positive and 89.8% HIV-negative completing their radiation dose and brachytherapy (radiotherapy involving insertion of radioactive source into the tissue) (p=0.03). For concurrent chemotherapy, only 53.1% HIV-positive and 74.6% HIV-negative managed to complete four or more weekly cycles. After 6 weeks, poor response to treatment was significantly associated with stage IIIB (OR=2.39, 95% CI 1.45-3.96), and receiving of less than recommended radiation dose (OR=3.14, 95% CI 1.24-7.94)[115].

Combination of radiotherapy and chemotherapy

A prospective quantitative comparative study in Zambia, evaluated the treatment response, treatment toxicities and compliance with radical chemo-radiation among both HIV-positive (median age of 40 years) and –negative (median age of 55 years) women with stage IB_2-IIIB cancer[116]. As opposed to failure to complete treatment as indicated by evidence in South Africa[115], all participants in this prospective study completed their treatments. Well selected HIV-positive cervical cancer patients on HAART can safely tolerate radical chemo-radiation in conventional doses[116]. The difference in chemo-radiation doses (6.5Gy x 4 for 58% of HIV-positive women vs. 8Gy x 3 for 58% of HIV-negative women) was significant in relation to

HIV status (p=0.022). In terms of toxicity (with regard to GIT system, skin, Haemopoietic system, and GU system) there was no significant differences between HIV-positive and –negative patients[116].

Surgery (radical hysterectomy)

Three case studies in South Africa of HIV-positive women with LVSI, an 18-year old nulliparous, 36-year old primiparous and 39-year old para-2, examined radical hysterectomy to inform management of early stage invasive cancer[121]. After 6 years post-surgery, the 18-year old has recovered and all the vaginal vault cytologic smears have been negative. At 3 years follow-up visits, both the 36- and 39-year olds have also recovered with negative vaginal vault cytologic smears[121].

4.3.5 Quality assessment of included studies

Few studies (n=2, 20.0%) were determined to be of 'high' quality using a combination of the modified Newcastle-Ottawa Quality Assessment Scale and the NIH Study Quality Assessment Tools for observational cohort cross-sectional case-control and before-after studies[81-82]. The majority of the studies (n=6, 60.0%) were of 'moderate' quality, and two (20.0%) were of 'low' quality. Adequate randomisation was conducted in both controlled interventions[113-114] and this provided confidence that reported results are attributable to the intervention than difference in groups. For the before-after studies, six out of seven studies had a control group[110-112,115-116,120], and this also provided confidence that the reported improvements between before and after evaluations are not mere chance. Two studies were mostly descriptive[119,121]. A few studies measured confounders adequately, with most rarely measuring them. In as much as outcomes were defined consistently across the studies, their validity and reliability was not well measured.

4.4 Results of the cross-sectional survey on knowledge, attitudes and practices of young people towards cervical cancer, risk factors, screening and HPV vaccination

This section presents results from the cross-sectional survey on knowledge, attitudes and practices of young people towards cervical cancer, risk factors, screening and HPV vaccination in Zimbabwe. This section's results are presented in five subsections. The first subsection presents the characteristics of the selected five provinces and descriptive statistics on response rates and socio-demographic characteristics of participants. The second subsection presents Cronbach's alpha values to assess and evaluate the internal consistency of the questionnaire responses. The third subsection presents univariate comparison of variables with the high school and university student groups. Descriptive statistics for the study samples were calculated without any adjustment for the complex sample design since the aim was simply to describe the samples. However, for analytical hypothesis testing and regression modelling the clustering inherent in the study design for the high school children was taken into account using Stata's survey ("svy") module.

The fourth section presents data related to knowledge, attitude and practices of young people towards cervical cancer. Subsection five presents the relationship between knowledge of cervical cancer, screening and HPV vaccination with socio-demographic characteristics of young people. Multiple logistic regression results of these relationships are presented. Post-regression tests for the quality of the regression models are also presented.

4.4.1 Descriptive statistics

4.4.1.1 Characteristics of the selected provinces

The following five provinces, Mashonaland West, Midlands, Masvingo, Manicaland and Harare, were selected for inclusion out of the ten provinces in Zimbabwe (see Figure 4.5). Harare has more than one university; therefore, random selection of one university was carried out as well as selection of two high schools.

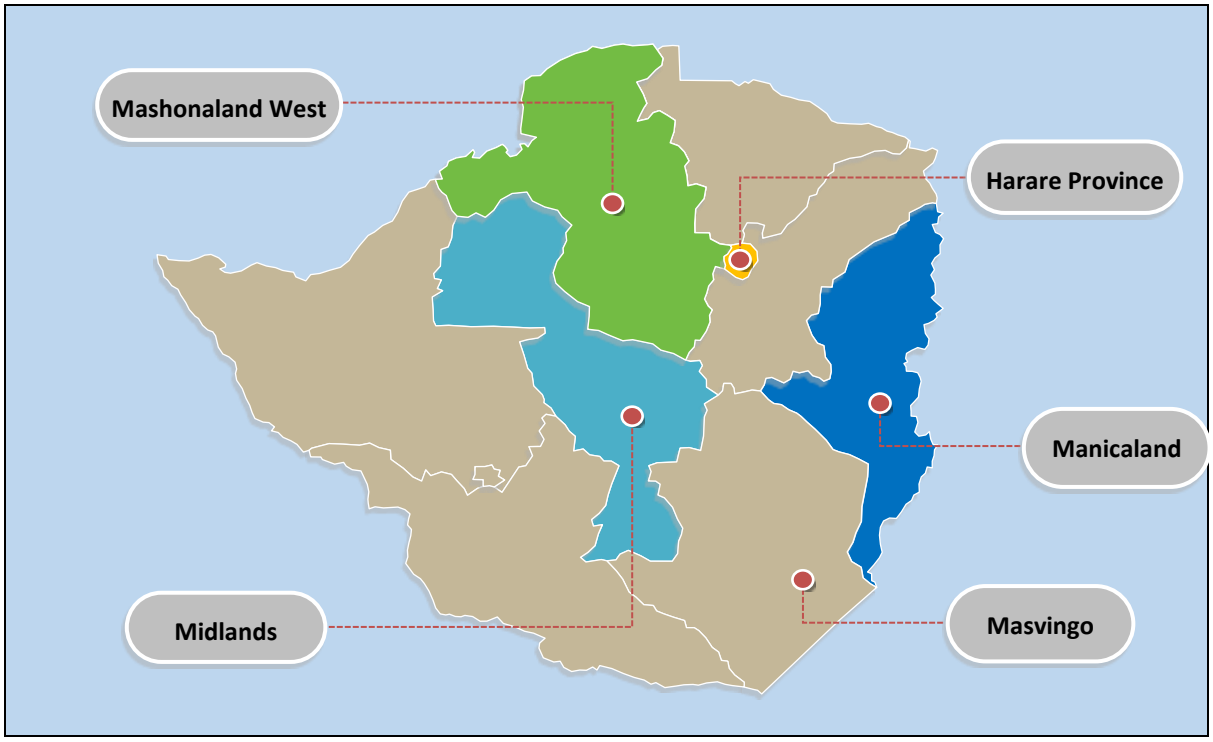

Figure 4.5: Map of the five selected provinces

Source of the editable map *https://yourfreetemplates.com/free-zimbabwe-editable-map/*

4.4.1.2 Response rates

I planned to interview a total of 978 participants, 531 high school and 447 university students. Purposive sampling was used to recruit university students resulting in 513 completing the interview, which is 66 more students interviewed than the initially targeted number. However, some high school students did not get interviewed (in all cases there was no reason given or lack of parental consent) (see Table 4.1). A total of 751 (238 high school and 513 university) students participated in the study. The response rate among the high school children was thus 238/531 = 44.82%.

Table 4.1: Non-response rate of high school students

Reason for non-response	Frequency	Percent (%)
No parental consent	202	68.94
No reason provided	91	31.06
Total	293	100.00

4.4.1.3 Socio-demographic characteristics of intended participants

The majority of the participants were females in both samples. Female students constituted 68.91% and 60.82% of the participants among high school and university samples, respectively (see Table 4.2). The participants' ages ranged from 15 to 21 years old among high schools and from 18 to 24 years among university students. Among high school students, those who were 15 (21.43%) and 18 (24.79%) years old, constituted the biggest numbers. Among university participants, 24.76% were 20 years old and only 10.72% were 24 years old (see Table 4.2).

Table 4.2: Distribution of gender and age of participants

Level of education	Frequency	Percentage (%)
High school students		
Female	164	68.91
Male	74	31.09
University students		
Female	312	60.82
Male	201	39.18

	Age	Harare		Manicaland		Mash. West		Masvingo		Midlands		Total	
		Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
High school students	15	22	30.99	0		6	14.29	6	13.64	17	43.59	**51**	**21.43**
	16	16	22.54	0		12	28.57	7	15.91	11	28.21	**46**	**19.33**
	17	18	25.35	0		12	28.57	7	15.91	4	10.26	**41**	**17.23**
	18	15	21.13	21	50.00	7	16.67	11	25.00	5	12.82	**59**	**24.79**
	19	0		19	45.24	4	9.52	13	29.55	2	5.13	**38**	**15.97**
	20	0		1	2.38	1	2.38	0		0		**2**	**0.84**
	21	0		1	2.38	0		0		0		**1**	**0.42**
	Total	**71**	**100.00**	**42**	**100.00**	**42**	**100.00**	**44**	**100.00**	**39**	**100.00**	**238**	**100.00**
University students	18	5	3.82	2	3.28	0		1	0.94	1	0.85	**9**	**1.75**
	19	32	24.43	19	31.15	6	6.19	3	2.83	15	12.71	**75**	**14.62**
	20	32	24.43	19	31.15	24	24.74	19	17.92	33	27.97	**127**	**24.76**
	21	31	23.66	8	13.11	24	24.74	22	20.75	25	21.19	**110**	**21.44**
	22	15	11.45	5	8.20	19	19.59	19	17.92	22	18.64	**80**	**15.59**
	23	8	6.11	4	6.56	10	10.31	20	18.87	15	12.71	**57**	**11.11**
	24	8	6.11	4	6.56	14	14.43	22	20.75	7	5.93	**55**	**10.72**
	Total	**131**	**100.00**	**61**	**100.00**	**97**	**100.00**	**106**	**100.00**	**118**	**100.00**	**513**	**100.00**

Most of the participants resided in high-density areas, with 55.46% of high school and 50.88% of university students (see Table 4.3). The majority of both high school (92.44%) and university (93.96%) students described themselves as Christians. Almost half of the university students, 49.51% (254/513) had ever consumed alcohol as compared to 12.61% (30/230) of high school students. Only 3.70% (19/513) of university students were married with 0.39% (2/513) having been widowed.

Table 4.3: Other socio-demographic characteristics of participants

High school students				University students			
		Frequency	Percent			Frequency	Percent
Province				**Province**			
	Harare	71	29.83		Harare	131	25.54
	Manicaland	42	17.65		Manicaland	61	11.89
	Mashonaland	42	17.65		Mashonaland	97	18.91
	Masvingo	44	18.49		Masvingo	106	20.66
	Midlands	39	16.39		Midlands	118	23.00
Residential area				**Residential area**			
	High density	132	55.46		High density	261	50.88
	Low density	53	22.27		Low density	184	35.87
	Rural area	53	22.27		Rural area	68	13.26
Religion				**Religion**			
	Christianity	220	92.44		Christianity	482	93.96
	Traditional	1	0.42		Traditional	4	0.78
	Apostolic sect	14	5.88		Apostolic	13	2.53
	Muslim	2	0.84		Muslim	6	1.17
	None	1	0.42		None	8	1.56
Ever taken alcohol				**Ever taken alcohol**			
	no	208	87.39		no	254	49.51
	Yes	30	12.61		Yes	259	50.49
Do you smoke				**Do you smoke**			
	No	237	99.58		No	480	93.57
	Yes	1	0.42		Yes	33	6.43
Marital status	Single	238	100.00	**Paid employment**			
					No	498	97.08
					yes	15	2.92
				Marital status	Single	492	95.91
					Married	19	3.70
					Widowed	2	0.39

4.4.1.4 Univariate comparison of sociodemographic characteristics

Univariate comparisons for the high school students were calculated with adjustment for the complex sample design. Therefore, the clustering inherent in the study design was taken into account using Stata's survey ("svy") module (see Table 4.4).

Table 4.4: Proportions comparisons among high school students

Adjusted Wald test results for proportions comparisons*

Alcohol drinking comparison among high school students (A vs. B)	n**	proportion of A	proportion of B	proportion (A-B)	p	95% Conf. Interval***	
Harare vs. Manicaland	202623	0.07	0.36	-0.29	<0.001	-0.38	-0.20
Harare vs. Mashonaland West	202623	0.07	0.02	0.05	0.270	-0.05	0.14
Harare vs. Masvingo	202623	0.07	0.09	-0.02	0.558	-0.11	0.07
Harare vs Midlands	202623	0.07	0.13	-0.06	0.156	-0.15	0.03
Manicaland vs. Masvingo	202623	0.36	0.09	0.27	<0.001	0.27	0.27
Manicaland vs. Mashonaland West	202623	0.36	0.02	0.34	<0.001	0.33	0.34

**Bonferroni adjusted alpha for criticality = 0.05/6 = 0.008*

***Adjusted for the complex sample design*

***lincom command used to generate 95% confidence intervals for the differences between the means*

Chi-squared test - Pearson designated-based F test estimates for proportions comparisons*

Alcohol drinking comparison among high school students (A vs. B)	n**	proportion of A	proportion of B	proportion (A-B)	p***
Male vs female	202623	0.067	0.074	-0.007	0,035
Smoker vs. non-smoker	202623	0.13	0.005	0.125	0,004

**Pearson's design-based F test estimates as indicated*

***Adjusted for the complex sample design*

****Bonferroni adjusted alpha for criticality = 0.05/2 = 0.025*

Univariate comparisons for university students were done without considering the sample design (see Table 4.5).

Table 4.5: Proportions comparison among university students

Z-test results for proportions comparisons*

Alcohol drinking comparison among university students (A-B)	n	proportion of A	proportion of B	proportion (A-B)	P	95% Conf. Interval	
Harare vs. Manicaland	513	0.47	0.54	-0.07	0.333	-0.23	0.08
Harare vs. Mashonaland West	513	0.47	0.53	-0.06	0.371	-0.19	0.07
Harare vs. Masvingo	513	0.47	0.45	0.02	0.845	-0.12	0.14
Harare vs Midlands	513	0.47	0.56	-0.09	0.140	-0.22	0.03
Manicaland vs. Masvingo	513	0.54	0.45	0.09	0.275	-0.07	0.24
Manicaland vs. Mashonaland West	513	0.54	0.53	0.01	0.853	-0.15	0.18

**Bonferroni adjusted alpha for criticallity = 0.05/6 = 0.008*

Fisher's exact two-tailed test results

Alcohol drinking comparison among university students	n	proportion of A	proportion of B	proportion (A-B)	P
Male vs female	513	0.64	0.42	0.22	<0.001
Smoker vs. non-smoker	513	0.94	0.48	0.46	<0.001
Students in paid employment vs. not in paid employment	513	0.53	0.50	0.03	>0.999
Smoking comparison among university students					
Male vs female	513	0.10	0.04	0.06	0.015
Alcohol drinker vs. non-alcohol drinker	513	0.12	0.008	0.11	<0.001
Students in paid employment vs. not in paid employment	513	0.20	0.06	0.14	0.065

Bonferroni adjusted alpha for criticallity = 0.05/2 = 0.025

4.4.2 Knowledge about the disease called cervical cancer

Most young people, 87.47% (656/750) claimed to know what the disease called cervical cancer is, with a mean score of 89.98% [95% CI 73.71.11-96.64] between high school and 86.72% [95% CI 83.48-89.40] among university students (see Table 4.6). There was no significance difference in mean scores between high school and university students (p=0.676).

*Table 4.6: Knowledge proportions between high school and university students**

Variable	Mean	Std.Err	Z	P>z	[95% Conf. Interval]	
High school students (n'=54)	.89	.020			0.74	.97
University students (n=512)	.87	.015			0.83	.89
Diff	.02	.045			-.07	.11
	under Ho:	.048	0.42	0.676		

For the high school students, the effective sample size (n' = 54) was used by diving n (238) by the design effect of 4.38

When asked how serious a disease cervical cancer is, 85.71% (204/238) of high school students gave an opinion of 'very serious', with only 2.94% (7/238) indicating 'not very serious'. Among university students, 84.80% (435/513) gave an opinion of 'very serious', with only 2.34% (12/513) indicating 'not very serious'.

4.4.2.1 Cronbach's Alpha for variables pertaining to knowledge of cervical cancer

Cronbach's alpha was calculated for the following variables pertaining to knowledge of cervical cancer and its risk factors: knowledge of cervical cancer risk factors, knowledge of perceived groups at high risk of developing cervical cancer, knowledge of cervical cancer treatment, and sources of cervical cancer knowledge. Knowledge of cervical cancer risk factors had a good internal consistency (α =0.82). The internal consistency for knowledge of perceived groups at high risk of developing cervical cancer and sources of cervical cancer knowledge, were also good. However, the internal consistency of knowledge of cervical cancer treatment was questionable (see Table 4.7).

Table 4.7: Reliability of variables

Subscales	Number of items	Cronbach's Alpha	Interpretation
Knowledge of cervical cancer risk factors	11	0.82	Good
Knowledge of perceived groups at high risk	8	0.78	Good
Knowledge of cervical cancer treatment	7	0.67	Questionable
Sources of cervical cancer knowledge	9	0.87	Good

4.4.3 Knowledge score for cervical cancer and its risk factors among high school and university students

Responses of three sections on knowledge were considered for calculating the knowledge score. The total score on knowledge was calculated by combining the scores of the following three sections: knowledge of cervical cancer risk factors, knowledge of perceived groups at high risk of developing cervical cancer, and knowledge of cervical cancer treatment. The maximum possible score for the knowledge of cervical cancer part was thus 11+8+7= 26 (see Table 4.8).

Table 4.8: Cervical cancer knowledge scores among high school and university students

Cervical cancer knowledge scores for high school students*			
Cervical cancer knowledge score	**Female**	**Male**	**Total**
Total scores (out of 26)	**Frequency (%)**	**Frequency (%)**	**Frequency (%)**
0	27(16.46)	9(12.16)	36(15.13)
1	18(10.98)	11(14.86)	29(12.18)
2	5(3.05)	3(4.05)	8(3.36)
3	4(2.44)	4(5.41)	8(3.36)
4	10(6.10)	4(5.41)	14(5.88)
5	9(5.49)	8(10.81)	17(7.14)
6	10(6.10)	1(1.35)	11(4.62)
7	18(10.98)	7(9.46)	25(10.50)
8	12(7.32)	4(5.41)	16(6.72)
9	8(4.88)	3(4.05)	11(5.00)
10	7(4.27)	5(6.76)	12(5.04)
11	6(3.66)	2(2.70)	8(3.36)
12	9(5.49)	3(4.05)	12(5.04)
13	8(4.88)	4(5.41)	12(5.04)
14	4(2.44)	4(5.41)	8(3.36)
15	5(3.05)	1(1.35)	6(2.52)
16	4(2.44)	1(1.35)	5(2.10)
Total (%)	**164 (100)**	**74(100)**	**238(100)**

**Chi-2 test, Pearson: Designed-based F(1, 5) = 0.0176, p = 0.900*

Cervical cancer knowledge scores for university students**			
Cervical cancer knowledge score	**Female**	**Male**	**Total**
Total scores (out of 26)	**Frequency (%)**	**Frequency (%)**	**Frequency (%)**
0	48(15.38)	39(19.40)	87(16.96)
1	48(15.38)	33(16.42)	81(15.79)
2	38(12.18)	15(7.46)	53(10.33)
3	16(5.13)	10(4.98)	26(5.07)
4	19(6.09)	18(8.96)	37(7.21)
5	16(5.13)	17(8.46)	33(6.43)
6	26(8.33)	13(6.47)	39(7.60)
7	20(6.41)	11(5.47)	31(6.04)
8	34(10.90)	15(7.46)	49(9.55)
9	16(5.13)	8(3.98)	24(4.68)
10	17(5.45)	5(2.49)	22(4.29)
11	8(2.56)	10(4.98)	18(3.51)
12	2(0.64)	2(1.00)	4(0.78)
13	0(0)	1(0.50)	1(0.19)
14	1(0.32)	0(0)	1(0.19)
15	0(0)	1(0.50)	1(0.19)
16	0(0)	1(0.50)	1(0.19)
17	1(0.32)	0(0)	1(0.19)
18	1(0.32)	0(0)	1(0.19)
20	1(0.32)	2(1.00)	3(1.00)
Total (%)	**312(100)**	**201(100)**	**513(100)**

***Fisher's exact two-tailed p-value = 0.324*

There was not much difference on comprehensive knowledge of cervical cancer and its risk factors, based on the calculated overall scores for both high school and university students (see Table 4.8). Only 12.80% (21/164) of high school female students managed a knowledge score about cervical cancer and its risk factors of 13 and above as compared to 13.51% (10/74) of high school male students. However, the difference in knowledge scores among the high school students was not statistically significant (p=0.900). This trend was also found among university students, with only 1.28% (4/312) of university female students scoring a knowledge score about cervical cancer and its risk factors of 13 and above as compared to 2.49% (5/201) of university male students. The difference in cervical cancer knowledge among university students was also not statistically significant (p=0.324).

Overall, only 43.14% (324/751) had ever heard of cervical cancer prevention or screening and 53.0% (398/751) did not know about HPV, how it is transmitted or prevented. Some of the students indicated that food, having sex with any uncircumcised male partner, smoking, and use of detergents such as bathing soaps and hair removers, are some of the factors contributing to the development of cervical cancer. These misconceptions were among both females and males as illustrated by responses from the participants:

> 23-year-old university female student suggested; "***I am no longer using bathing soap on my reproductive organ because it contributes to the development of cervical cancer***";
>
> Whilst another 21-year-old female university student suggested, "***having sex with an uncircumcised male partner is dangerous and I wish all men will answer the call to be circumcised so that women will not have to worry about cervical cancer***".

4.4.4 Factors associated with knowledge of cervical cancer and its risk factors among high school and university students

Multiple variable logistic regression modelling was used to determine the adjusted association between knowledge of cervical cancer and the following factors; age, gender, residence, drinking alcohol, smoking, parents' education and province. Since 92.44% (220/238) of high school students and 93.96% (482/513) of university students reported religion to be Christianity, we decided not to include religion in the regression modelling. On being predictors of knowledge of cervical cancer, most of these socio-demographic characteristics were not statistically significant.

High school students with parents educated up to O-levels (OR= 2.5; 95% CI= 1.28 – 4.93) and a qualification below degree (OR= 3.13; 95% CI= 1.15 – 8.49), were almost 3 times more likely to have higher knowledge scores about cervical cancer as compared to high school students with parents with a university degree or a primary level education (see Table 4.9). In addition, high school students in Mashonaland West (OR= 2.77; 95% CI= 1.60 – 4.80) and Midlands (OR= 1.77; 95% CI= 1.06 – 2.95) provinces were 2 to 3 times more likely to have higher knowledge scores about cervical cancer as compared to high school students in Harare province (see Table 4.9).

Table 4.9: Factors associated with knowledge of cervical cancer among high school students

Factors associated with knowledge of cervical cancer among high school students									
High school students*		**Univariate model**		**Full model**		**Final model**			
Main variable		**Odds Ratio**	**p**	**Odds Ratio**	**p**	**Odds Ratio**	**p**	**95% Conf. Interval**	
parents education	Reference grp(University degree**)								
	O-levels	2.86	0.007	2.51	0.017	2.51	0.017	1.28	4.92
	Qualification below degree	3.01	0.029	3.13	0.033	3.13	0.033	1.15	8.49
	A-levels	3.18	0.048	3.01	0.069	3.01	0.069	0.88	10.25
	No formal education	3.20	0.351	3.00	0.406	3.00	0.406	0.13	68.02
province	Reference grp(Harare)								
	Mashonaland West	2.28	0.019	2.77	0.005	2.56	0.009	1.59	4.80
	Midlands	1.76	0.052	1.77	0.034	1.64	0.067	1.06	2.95
	Manicaland	1.31	0.280	1.63	0.094	1.63	0.094	0.89	2.98
	Masvingo	1.24	0.374	1.45	0.127	1.45	0.127	0.86	2.43
residence	Reference grp(High-density)								
	Rural	1.36	0.402						
	Low-density	0.89	0.565						
age**		1.21	0.494						
drinking alcohol		0.72	0.670						
gender		1.06	0.900						

**Clustering inherent in the study design was taken into account and regression was done using Stata's survey ("svy") module for high school students.*
***Primary level was combined with University degree since there was no difference between the two levels of education*
****Age as a continuous variable is liner in relation to the logit (Box-Tidwell test p-value = 0.735)*

Post regression test, using the Pearson's goodness-of-fit test was carried out without factoring the complex sample design- Pearson's GOF p-value = 0.430..

Among the university students, those who smoke, were almost 8 times likely to have higher knowledge scores about cervical cancer as compared to those who did not smoke (OR=7.80; 95% CI= 1.29 – 47.21). In addition, university students in Harare and Mashonaland West, were more likely to have higher knowledge scores about cervical cancer as compared to the students in Midlands, Masvingo and Manicaland. However, these observed differences among provinces were not statistically significant (see Table 4.10).

Table 4.10: Factors associated with knowledge of cervical cancer among university students

Factors associated with knowledge of cervical cancer among university students									
University students		**Univariate model**		**Full model**		**Final model**			
Variable		**Odds Ratio**	**p**	**Odds Ratio**	**p**	**Odds Ratio**	**p**	**95% Conf. Interval**	
smoker		4.36	0.074	7.80	0.025	7.80	0.025	1.29	47.21
residence	Reference grp(High-density)								
	Low-density	4.37	0.073	4.25	0.085	4.25	0.085	0.82	22.02
	Rural	1.93	0.593	2.12	0.554	2.12	0.554	0.18	25.47
province	Reference grp(Harare*)								
	Midlands	0.18	0.113	0.13	0.079	0.13	0.079	0.01	1.26
	Masvingo	0.20	0.137	0.17	0.122	0.17	0.122	0.02	1.62
	Manicaland	0.35	0.332	0.28	0.250	0.28	0.250	0.03	2.46
age**		0.79	0.300						
drinking alcohol		0.48	0.309						
gender		1.96	0.319						

**Mashonaland West was combined with Harare since there was no difference between the two provinces*

**Age as a continuous variable is liner in relation to the logit (Box-Tidwell test p-value = 0.241)

Post regression tests were conducted to check the model fit. Area under the ROC curve = 0.70 for the final model; Hosmer and Lemeshow Goodness of fit test p-values = 0.09; 0.12 and 0.17 respectively (8, 10 and 12 groups)

4.4.5 Cervical cancer attitudes and care-seeking behaviour

Majority of the participants, 94.27% (708/751), acknowledged that young people should be concerned about cervical cancer, with a mean score of 90.30% [95% CI= 85.08 - 92.59] among high school students and 96.20% [95% CI= 94.75 - 97.63] among university students. The mean concern for cervical cancer score was not statistical significance (p=0.062) between high school and university students (see Table 4.11).

*Table 4.11: Concern about cervical cancer proportions between high school and university students**

Variable	Mean	Std.Err	z	P>z	[95% Conf. Interval]	
High school students (n'=45)	.90	.042			0.85	.93
University students (n=513)	.96	.008			0.95	.98
Diff	-.06	.046			-.150	.029
	under Ho:	.032	-1.86	0.062		

For the high school students, the effective sample size (n' = 45) was used by diving n (238) by the design effect of 5.21

4.4.5.1 Cronbach's Alpha for variables pertaining to attitude towards cervical cancer

Cronbach's alpha was calculated for the following variables pertaining to young people's attitude towards cervical cancer and care-seeking behaviour: perceived attitude towards cervical cancer and perceived health seeking behaviour. The internal consistency for perceived attitude towards cervical cancer (0.74) and perceived feelings towards people with cervical cancer (0.73) was acceptable whilst for perceived health seeking behaviour was good, at 0.89 (see Table 4.12).

Table 4.12: Reliability of variables

Subscales	Number of items	Cronbach's Alpha	Interpretation
Perceived attitude towards cervical cancer	5	0.74	Acceptable
Perceived feelings towards people with cervical cancer	6	0.73	Acceptable
Perceived health seeking behaviour	6	0.89	Good

4.4.6 Positive attitude towards cervical cancer scores among high school and university students

Responses of three sections on attitude towards cervical cancer and care-seeking behaviour were considered for calculating the positive attitude score. The total score on positive attitude towards cervical cancer was calculated by combining the scores of the following three sections: perceived attitude towards cervical cancer, perceived feelings towards people with cervical cancer, and perceived health seeking behaviour. The maximum possible score for the knowledge of cervical cancer part was thus 5+6+6= 17 (see Table 4.13).

Table 4.13: Positive attitude towards cervical cancer scores among participants

Attitude towards cervical cancer scores for high school students*			
Attitude towards cervical cancer score	**Female**	**Male**	**Total**
Total scores (out of 17)	**Frequency (%)**	**Frequency (%)**	**Frequency (%)**
0	1(0.61)	0(0)	1(0.42)
1	4(2.44)	2(2.70)	6(2.52)
2	36(21.95)	12(16.22)	48(20.17)
3	13(7.93)	4(5.41)	17(7.14)
4	4(2.44)	2(2.70)	6(2.52)
5	7(4.27)	0(0)	7(2.94)
6	9(5.49)	1(1.35)	10(4.20)
7	6(3.66)	4(5.41)	10(4.20)
8	5(3.05)	4(5.41)	9(3.78)
9	9(5.49)	7(9.46)	16(6.72)
10	8(4.88)	9(12.16)	17(7.14)
11	9(5.49)	7(9.46)	16(6.72)
12	18(10.98)	7(9.46)	25(10.50)
13	22(13.41)	8(10.81)	30(12.61)
14	6(3.66)	5(6.76)	11(4.62)
15	5(3.05)	0(0)	5(2.10)
16	2(1.22)	1(1.35)	3(1.26)
17	0(0)	1(1.35)	1(0.42)
Total	**164(100)**	**74(100)**	**238(100)**

**Chi-2 test, Pearson: Designed-based F(1, 5) = 11.95, p = 0.018*

Attitude towards cervical cancer scores for university students**			
Attitude towards cervical cancer score	**Female**	**Male**	**Total**
Total scores (out of 17)	**Frequency (%)**	**Frequency (%)**	**Frequency (%)**
0	1(0.32)	0(0)	1(0.19)
1	14(4.49)	9(4.48)	23(4.48)
2	88(28.21)	51(25.37)	139(27.10)
3	33(10.58)	25(12.44)	58(11.31)
4	30(9.62)	16(7.96)	46(8.97)
5	22(7.05)	15(7.46)	37(7.21)
6	13(4.17)	9(4.48)	22(4.29)
7	11(3.53)	7(3.48)	18(3.51)
8	13(4.17)	6(2.99)	19(3.70)
9	5(1.60)	4(1.99)	9(1.75)
10	11(3.53)	4(1.99)	15(2.92)
11	11(3.53)	14(6.97)	25(4.87)
12	12(3.85)	9(4.48)	21(4.09)
13	15(4.81)	9(4.48)	24(4.68)
14	14(4.49)	9(4.48)	23(4.68)
15	12(3.85)	5(2.49)	17(3.31)
16	4(1.28)	6(2.99)	10(1.95)
17	3(0.96)	3(1.49)	6(1.17)
Total	**312(100)**	**201(100)**	**513(100)**

***Fisher's exact two-tailed p-value = 0.427*

There was not much difference on positive attitude towards cervical cancer, based on the calculated overall scores for both high school and university students (see Table 4.13). Almost half, 48.17% (79/164) of high school female students managed a positive attitude score towards cervical cancer of 9 and above as compared to 60.81% (45/74) of high school male students. This difference in positive attitude scores towards cervical cancer among the high school students was statistically significant (p=0.018). Among university students, 27.88% (87/312) of university female students had a positive attitude score towards cervical cancer of 9 and above as compared to 31.34% (63/201) of university male students. The difference in positive attitude scores among university students was however not statistically significant (p=0.427).

When the respondents were asked on perceived risk of them or their girlfriend or wife (in the case of male respondents) developing cervical cancer, 45.34% (258/569) indicated no perceived risk. Some of the reasons that prompted the no perceived risk were as follows; not being an alcohol drinker or smoker, not using contraceptive pill, having been circumcised or having a circumcised partner, going for regular medical check-ups, being faithful to my partner, not HIV positive, by praying and not being a commercial sex worker.

> "***I am not worried about cervical cancer neither is my girlfriend because I am circumcised and we are both faithful***", wrote 23 year old male university student.
>
> Whilst a 24 year old female university student wrote, "***commercial sex workers and those who drink alcohol or use drugs are the ones that are at likely to develop cervical cancer not me since I am a Christian***".

Some of the respondents (both males and females) indicated that it is solely the responsibility of those 'who are likely to develop cervical cancer to seek for cervical cancer prevention'.

> "***If I am not mistaken, cervical cancer is a women's disease, so women should be the ones to be responsible and take good care of their health***", suggested 18 year old male high school student.

Other respondents believed that women who develop cervical cancer are of 'loose morals' and 'ignorant'.

> "***I am very particular when it comes to my health; I go for regular check-ups. Women who develop cervical cancer are ignorant***", wrote a 23 year old female university student.

When asked on what worries them most about cervical cancer, the students indicated that cervical cancer is associated with dying; the expensive nature of the treatment; the stigma that society attaches to cervical cancer; failure to conceive; divorce; the suffering and pain that the patient and their families undergo.

> "***What worries me most about cervical cancer is that the patient will obviously die because the cure is expensive***", suggested 15 year old female high school student;
>
> Whilst a 21 year old male university student wrote, "***what worries me most is if my girlfriend or wife is to have cervical cancer then I will not have sex and she will not be able to bear children for me. That can be a recipe for separation***".

4.4.7 Factors associated with a positive attitude towards cervical cancer among high school and university students

Multiple variable logistic regression modelling was used to determine the adjusted association between positive attitude towards cervical cancer and the following factors; age, gender, residence, drinking alcohol, smoking, parents' education and province. Religion was included in the regression modelling. Almost no socio-demographic characteristics were statistically associated with a positive attitude towards cervical among high school and university students. High school students with parents educated up to primary level were 84% more likely not to have positive attitude towards cervical cancer (OR= 0.16; 95% CI= 0.06 – 0.48) as compared to high school students with parents with a university degree (see Table 4.14).

Table 4.14: Factors associated with a positive attitude towards cervical cancer among high schools students

Factors associated with positive attitude towards cervical cancer among high school students									
High school students*		**Univariate model**		**Full model**		**Final model**			
Main variable		**Odds Ratio**	**p**	**Odds Ratio**	**p**	**Odds Ratio**	**p**	**95% Conf. Interval**	
age**		1.43	0.010	1.36	0.060	1.36	0.060	0.98	1.89
Gender		1.65	0.018	2.11	0.057	2.11	0.057	0.97	4.63
Province	Reference grp(Harare)								
	Manicaland	1.81	0.027	0.82	0.474	0.82	0.474	0.42	1.59
	Mashonaland West	1.64	0.029	1.67	0.025	1.67	0.025	1.10	2.54
	Masvingo	1.78	0.030	1.32	0.176	1.32	0.176	0.84	2.08
	Midlands	0.77	0.231	0.71	0.154	0.71	0.154	0.41	1.20
parents education	Reference grp(University degree)								
	Primary level	0.14	0.002	0.16	0.007	0.16	0.007	0.06	0.48
	No formal education	0.24	0.158	0.15	0.225	0.15	0.225	0.01	5.05
	A-levels	0.58	0.355	0.75	0.663	0.75	0.663	0.15	3.80
	Qualification below degree	1.19	0.709	1.32	0.561	1.32	0.561	0.42	4.14
	O-levels	0.91	0.783	0.91	0.815	0.91	0.815	0.34	2.42
drinking alcohol		0.76	0.566						
Residence	Reference grp(High density)								
	Low density	1.17	0.633						
	Rural	0.93	0.813						

**Clustering inherent in the study design was taken into account and regression was done using Stata's survey ("svy") module for high school students.*

***Age as a continuous variable is liner in relation to the logit (Box-Tidwell test p-value = 0.512)*

Post regression test, using the Pearson's goodness-of-fit test was carried out without factoring the complex sample design- Pearson's GOF p-value = 0.182.

Among the university students, those in Harare were more likely to have higher positive attitude scores towards cervical cancer as compared to the students in Midlands, Mashonaland West, Masvingo and Manicaland. For example, university students in Midlands were 55% more likely not to have positive attitude towards cervical cancer as compared to students in Harare (OR= 0.45; 95% CI= 0.25 – 0.81) and this difference was statistically significant (p=0.007). University students with parents who had a qualification below university degree, A-levels, O-levels or no formal education, were more likely to have a higher positive attitude towards cervical cancer as compared to students with parents with a university degree. However, these observed differences were not statistically significant (see Table 4.15).

Table 4.15: Factors associated with a positive attitude towards cervical cancer among university students

Factors associated with positive attitude towards cervical cancer among university students									
University students		**Univariate model**		**Full model**		**Final model**			
	Variable	**Odds Ratio**	**p**	**Odds Ratio**	**P**	**Odds Ratio**	**p**	**95% Conf. Interval**	
Province	Reference grp(Harare)								
	Midlands	0.46	0.007	0.45	0.007	0.45	0.007	0.25	0.81
	Mashonaland West	0.65	0.148	0.65	0.142	0.65	0.142	0.36	1.16
	Masvingo	0.81	0.443	0.80	0.428	0.80	0.428	0.46	1.39
	Manicaland	0.87	0.676	0.92	0.808	0.92	0.808	0.48	1.78
parents education	Reference grp(University degree)								
	Qualification below degree	1.59	0.057	1.65	0.043	1.65	0.054	0.99	2.64
	No formal education	2.01	0.126	1.94	0.151	1.94	0.151	0.79	4.82
	A-levels	1.45	0.346	1.52	0.299	1.52	0.299	0.69	3.33
	Primary level	0.65	0.582	0.66	0.604	0.66	0.604	0.14	3.16
	O-levels	1.16	0.593	1.19	0.538	1.19	0.538	0.68	2.10
smoker		0.63	0.298						
gender		1.18	0.401						
drinking alcohol		1.09	0.660						
residence	Reference grp(High-density)								
	Low-density	1.06	0.792						
	Rural	1.03	0.913						
age**		1.00	0.948						

***Age as a continuous variable is liner in relation to the logit (Box-Tidwell test p-value = 0.635)*

Area under the ROC curve = 0.61 for the final model; Hosmer and Lemeshow Goodness of fit test p-values = 0.34; 0.51 and 0.30 respectively (8, 10 and 12 groups)

4.4.8 Cervical cancer awareness and need for more information among high school and university students

A quarter of the young people in this study reported to feeling well informed about cervical cancer, mean scores of 24.43% [95% CI= 17.14-32.92] and 26.12% [95% CI 22.32-29.92%] among high school and university students, respectively. There was no significance (p=0.586) between the two mean scores of feeling well informed about cervical cancer (see Table 4.16).

*Table 4.16 High school and university students reported feeling of well informed about cervical cancer**

Variable	Mean	Std.Err	Z	P>z	[95% Conf.	Interval]
High school students (n'=194)	0.24	0.031			0.17	0.33
University students (n=513)	0.26	0.019			0.22	0.30
Diff	-0.02	0.036			-0.091	0.051
	under Ho:	0.037	-0.54	0.586		

For the high school students, the effective sample size (n' = 194) was used by diving n (238) by the design effect of 1.23

However, some of the young people who claimed to feeling well informed about cervical cancer, also wished for more cervical cancer information, a mean score of 98.09% [95% CI= 92.97-99.50] among high school students and 96.30% [95% CI= 93.66-97.93%] among university students. The mean scores were also not significant (p=0.196) between the two groups (see Table 4.17).

Table 4.17: High school and university students wish for more cervical cancer information

Variable	Mean	Std.Err	Z	P>z	[95% Conf.	Interval]
High school students (n'=192)	0.98	0.010			0.93	1.00
University students (n=513)	0.96	0.008			0.94	0.98
Diff	0.02	0.013			-0.006	0.046
	under Ho:	0.015	1.29	0.196		

For the high school students, the effective sample size (n' = 192) was used by diving n (238) by the design effect of 1.24

4.4.9 Factors associated with the need for more cervical cancer information among high school and university students

Logistic regression modelling failed to uncover any meaningful relationships between the measured potential explanatory variables and the perceived need for more cervical cancer information among high school and university students. The logistic regression models contained no statistically significant explanatory variables and areas under the ROC curve were all less than 0.35. The model F-tests were also non-significant.

CHAPTER FIVE: DISCUSSION

Note: Some of the discussion in this chapter has been published in BMC Systematic Reviews Journal (see Appendix 19).

5.1 Introduction

The purpose of this research was to synthesise and document published evidence relating to the available cervical cancer prevention and treatment modalities for HIV-seropositive women in developing countries; and investigate the knowledge, attitudes and practices of young people (15 to 24 years old) in Zimbabwe about cervical cancer, screening, HPV, and vaccination. This chapter brings together the discussion of the results that were generated by the two systematic reviews and the cross-sectional survey. A number of key findings have been reported to explain the current screening and treatment modalities that are in use for HIV-seropositive women with cervical cancer in developing countries. Although the systematic reviews covered developing countries, the idea of the synthesised evidence was to help explain the epidemiology and current cervical cancer management concerning Zimbabwe. Besides providing synthesised evidence on HIV-seropositive women with cervical cancer, the research laid the groundwork for ideas that can be embraced by Zimbabwe in tightening cervical cancer prevention and management, by reporting on the knowledge, attitude and practices of young people towards cervical cancer, screening, HPV and vaccination. It can be argued that the knowledge and attitude of young people towards cervical cancer can have a bearing on the strategies that the government rolls out as well as the strategies' successes. This chapter is structured in an integrative approach to try to bring together the meaning and potential impact of the findings of this research.

5.2 Cervical cancer screening among HIV-seropositive women

The high-risk rate that HIV-seropositive women have towards developing cervical cancer renders the lack of specific evidence on which cervical cancer screening method is suitable and effective for them, a public health challenge. This study attempts to offer evidence on which cervical cancer screening approach or method is 'better' for HIV-seropositive women in developing countries and offer policymakers and health leadership a base to formulate solid screening guidelines.

This study has shown that there is not yet a standard screening method or tool for cervical cancer screening among HIV-seropositive women because each method has its benefits and risks that require to be considered when using it. However, this risk-benefit scale is usually considered secondary in developing countries because the availability of a screening method, whether effective or not, is important. In addition, this research has shown that there is no better screening method that fits the healthcare system of every developing country because priorities, resources and implementation of guidelines are different. Since all the cervical cancer screening methods being used for HIV-positive women are the same for HIV-negative women, careful analysis of each method's risks and benefits is required to help decisions on which method to use in the meantime as further research is conducted to find the 'best' screening method.

Due to challenges in establishing Pap smear as a national screening programme as has been done in developed countries, the use of VIA as the screening method of choice among both HIV-positive and HIV-negative women has increased significantly in developing countries[13,122]. In as much as VIA is being used more often because of its easy applicability even by nurses, evidence has shown that the use of VILI can increase the efficacy and accuracy among HIV-positive women[85,95]. The performance of VIA was reported to be much better in HIV-negative than HIV-positive women[85] and there are more high false positive rates among

HIV-positive women[99,103]. These findings might indicate that sequential screening using both VIA and VILI may be beneficial among HIV-seropositive women (see proposed opportunities for screening HIV-seropositive women in Figure 5.1). The sequential use of VIA and VILI has indicated a better clinical performance and risk-benefit balance when compared to their use individually[85] and this might be a combination method that developing countries can use for HIV-seropositive women. However, VILI's use in developing countries is not on the same scale as that of VIA because of the cost issues associated with iodine when compared to acetic acid. In addition, lessons learnt from Ethiopia indicated that implementation of visual-based screening methods among HIV-seropositive women requires provider initiation as a complimenting element[123].

As the implementation of VIA and VILI continue to grow in developing countries, the risks of misdiagnosing associated with visual inspection methods (VIA and VILI) should be carefully monitored among HIV-seropositive to prevent subjecting these women to unnecessary treatment as well as waste resources. This is supported by synthesised evidence from a review of the visual inspection methods[122]. Therefore, developing countries may be better off using VIA and VILI as screening tools, not as diagnostic tests. In addition, the see-see-and treat combination using VIA or VILI coupled with colposcopy and treating with cryotherapy has the potential of significantly reducing false positives and preventing over treating in clients who will not need cryotherapy[103].

Detecting of HR-HPV has been shown to be an effective secondary screening method for cervical cancer among HIV-seropositive, with almost all the HPV tests indicating better clinical performance when compared to cytology-based and visual based tests[88-90,92-93,95,101,104-105]. With long-term persistent infection with HPV almost always associated with the development of cervical cancer[124-127], emerging evidence suggests HPV testing as a better way as compared to cytology-based or visual screening methods[128]. A sequential screening of cervical cancer using

VIA or VILI and HPV testing maybe ideal in developing countries as this will reduce the number of false positive results[95] hence might limit resources and prevent subjecting women to unnecessary treatments (see Figure 5.1). This combination of VIA or VILI and HPV testing has the potential to offer a better benefits-risks balance when compared to other available screening methods currently being used for HIV-seropositive women. However, for developing countries to implement such a change, resources, guidelines and policies (which are context specific) will need to be made available in line with emerging scientific evidence. In addition, the safety interpretation of results of HPV tests requires trained professional to limit overestimation of precancerous lesions in HIV-seropositive women, which may result in unnecessarily subjecting women to treatment that they do not need as well as waste the limited resources. Therefore, this requires training of healthcare workers when implementing HPV testing.

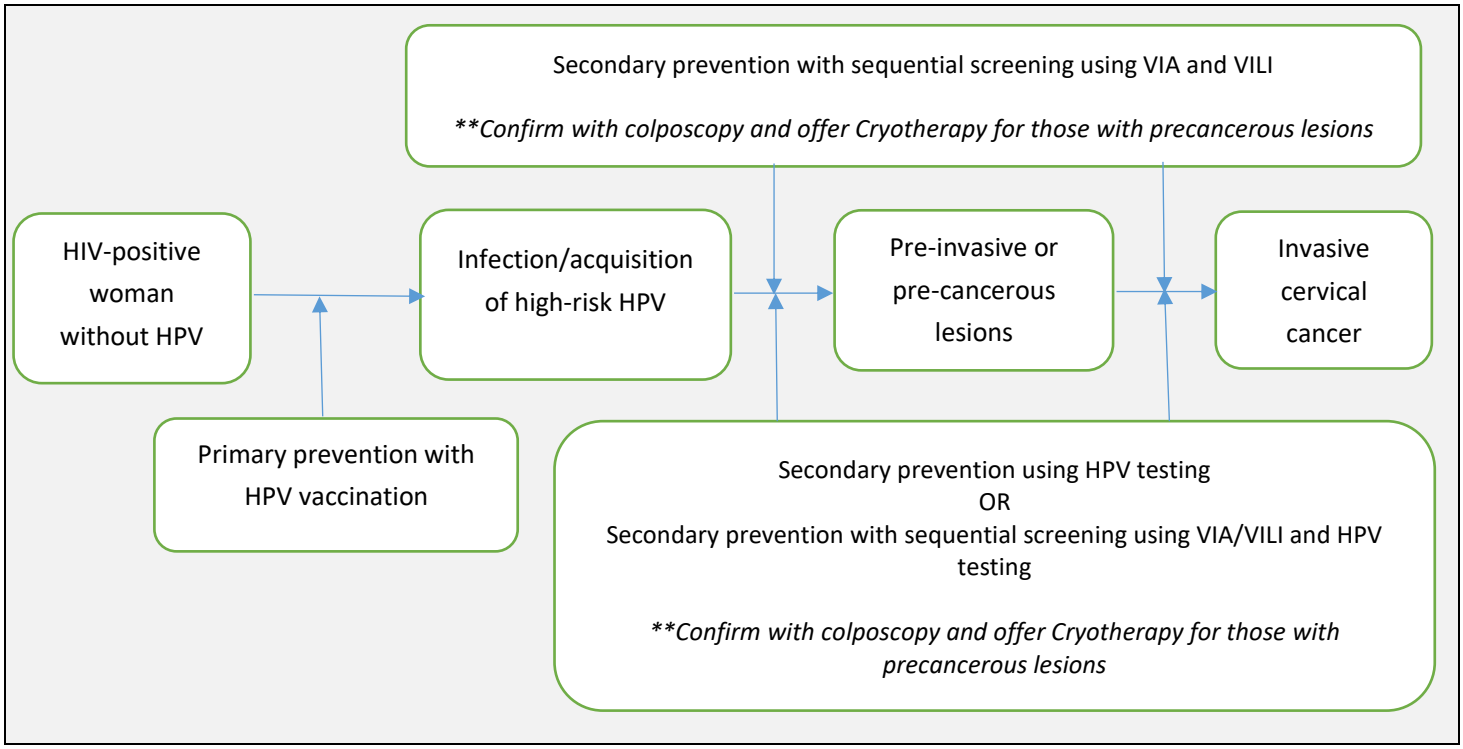

Figure 5.1: Proposed opportunities for prevention of cervical cancer in HIV-seropositive women

** Treatment with cryotherapy or LEEP should be offered after when results are verified by qualified personnel to limit subjecting these patients to unnecessary treatments verify results

HPV – Human papillomavirus; VIA – Visual inspection with acetic acid; VILI – Visual inspection with Lugol's iodine; LEEP - Loop Electrosurgical Excision Procedure

With improved knowledge and understanding of cervical cancer and HPV, several studies[129-134] have indicated the immunogenicity and safety of the currently used HPV vaccine among young and middle-aged HIV-seropositive women. There is scanty data on the implementation of the HPV vaccination, its efficacy and uptake among HIV-positive women as the available evidence focuses on safety and immunogenicity[129-135]. However, guidelines by the Centers for Disease Control and Prevention, and HIV Medicine Association of Infectious Diseases Society of America recommends HPV vaccination among young HIV-seropositive women aged 13 to 26 years[136]. Most developing countries have embarked on mass HPV vaccination of young girls and opportunities for effective and sustainable implementation of the vaccine among HIV-positive young girls exists and should be utilised. As the implementation of the mass HPV vaccination intensifies in developing countries, opportunities to increase the age of recipients to include young women (from 15 years old) and middle-aged HIV-seropositive women should be explored and initiated as suggested in Figure 5.1.

5.3 Cervical cancer treatment among HIV-seropositive women

The following treatments were evaluated: LEEP, cryotherapy, radiation including brachytherapy, chemotherapy, chemoradiation, and surgery. Treated patients ranged from those with low-grade cervical neoplasia to those with advanced stage IVB cervical cancer.

The introduction of life-long antiretroviral (ART) has been found to moderately reduce HPV infection incidences[137]. Despite the moderate effect on HPV infection, ART is prolonging the life span of those infected with HIV, thereby granting time for development of cervical cancer especially in countries with not well-established cervical cancer screening programmes. As such, available data concerning cervical cancer continues to show that HIV-seropositive women are 2 to 12 times more prone to developing cervical cancer[2,138]. This study has confirmed that the available treatments for both cervical neoplasia and cervical cancer (if detected early) among HIV-seropositive women are effective. However, clinical,

methodological and statistical heterogeneity, such as participants' baseline characteristics, immunosuppressive status, follow-up time, randomisation versus non-randomisation, samples sizes, and statistical calculations, among the 12 studies analysed, might explain some the differences in the findings. In this study, almost all the included studies had HIV-seropositive women who were of a younger age than HIV-negative women were.

This research has demonstrated that LEEP and cryotherapy treatments have the possibility of reducing progression from LSIL to HSIL as well as causing regression of cervical neoplasia. A randomised controlled trial in South Africa comparing cryotherapy with LEEP showed both treatments to be effective in reducing CIN2+ in HIV-seropositive women by over 70% within 12 months and that there were no significant differences between their efficacy[114]. Furthermore, the treatment failures observed in both cryotherapy and LEEP within 12 months were almost similar[114]. These findings were supported by another randomised controlled trial in South Africa, which showed that cryotherapy treatment of CIN1 reduces progression to CIN2+ (69% reduced regression, 95% CI: 58% to 83%, p=0.0001)[113]. However, this treatment benefit was exclusively significant among women with high-risk HPV and might point to a need for further multicentre research to explore the reasons for such a finding.

Three studies done in Thailand and Kenya demonstrated both the safety and effectiveness of LEEP treatment in HIV-seropositive women[110-112]. After 6 and 12 months of undergoing LEEP treatment, over 88.0% of HIV-seropositive women with cervical neoplasia were disease-free and this outcome was comparable to HIV-negative women[111]. Due to a short follow-up period of 12 months, these findings from Thailand differ from what has been reported when 73.0% of HIV-seropositive developed a recurrence of cervical neoplasia within 24 months follow-up[139]. In as much as LEEP was reported to be safe, a number of complications, such as severe intraoperative haemorrhage, early and late postoperative haemorrhage, localised infection of the cervix, and cervical stenosis were experienced in both HIV-positive and –negative women

although the difference was insignificant (p=0.24)[111]. Despite no difference in complications between HIV-positive and –negative women, further research on reasons for such complications need to be assessed and explored to inform best clinical practices.

A prospective cohort study conducted in Kenya estimating the safety, tolerability, and acceptability of LEEP for women with CIN 2/3, found almost consistent findings on safety and acceptability among HIV-seropositive women[110]. However, findings in Kenya indicated that symptoms of complications due to LEEP were more significant (419 cells/mm3 vs. 349 cells/mm3, $p<0.05$) in women with higher mean CD4+ count[110]. However, data on baseline characteristics of these women, such as age and how long some were on HAART was not available to help identify the reasons behind such a finding. In Thailand, another prospective study[112] identified slightly tangent results to those found in Kenya, when it reported that HIV-infection was not associated with LEEP complications and this finding was statistically insignificant (Adj OR = 0.41; 95% CI, 0.15-1.15, p=0.10). Different participants' selection and small sample sizes, age and follow-up periods among the three studies[110-112], might have had a bearing on the slightly different results. Therefore, further critical assessment of these different findings requires multicentre studies with long follow-up periods to help answer all the key questions on LEEP complications among HIV-seropositive women with cervical neoplasia.

Most HIV-seropositive patients in the studies assessing cervical cancer treatment were of a younger age and had a more advanced disease as compared to HIV-negative patients. In India, treatment with radiotherapy was seen to be effective among HIV-seropositive women with cervical cancer stage IIIB-IVA, as 50.0% of those who completed treatment achieving complete response[117] and these findings were supported by evidence from Kenya[118]. However, the associated acute treatment toxicity of radiotherapy among HIV-positive women was seen to be an independent significant risk factor [Adj RR=2.2] that interrupt or delays treatment resulting in most of these women not completing their prescribed treatments[118]. Acute

gastrointestinal, skin and genitourinary tract toxicities are the most prominent radiation-related acute toxicities and are associated with HIV[117-118]. These multisystem acute toxicity findings are in contrast to what was identified in a radical chemoradiation prospective study which reported no statistical significance differences between HIV-positive and –negative patients[116]. Therefore, further studies examination patients' baseline characteristics such as time of HAART or CD4+ counts will need to be conducted to analyse why studies are reporting different findings.

Being HIV-seropositive prevents the success of radiotherapy as most patients will not complete prescribed treatment due to associated multisystem toxicities hence resulting in poor response and outcomes in some cases. After 7 months post-radiotherapy, HIV-seropositive women were 3.1 times likely to have a residual tumour as compared to HIV-negative (p=0.0014)[118]. These findings indicate that completing radiation is a predictor of treatment response among HIV-seropositive women[115,140]. Palliative radiotherapy fractionation has been reported to be effective in HIV-seropositive patients with poor performance and advanced cancer[118] but having an intact immune system and a higher CD4+ count is a positive indicator to treatment response and reduction of tumour[120]. However, the small numbers involved in this study requires further multi-centre studies to be conducted to support evidence-informed treatment and the development of guidelines to further manage the prevention of treatment failure in HIV-seropositive women.

Despite completing prescribed treatment being an indicator of treatment response in radiotherapy[117-118], evidence on chemotherapy indicates that treatment completion did not have greater effect or impact on the response after six weeks as compared to radiotherapy[115]. In addition, cervical cancer stage IIIB was indicated to be associated with poor chemo-radiation after six weeks (OR=2.39, 95% CI 1.45-3.96)[115] and this might suggest that offering a full dose of radiation coupled with good medical care in terms of associated toxicities[117-118] might be

beneficial to HIV-seropositive with advanced cervical cancer. This suggestion is supported by findings that show that chemo-radiation incremental benefit as compared to radiotherapy is minimal[141]. However, these findings required further studies to be conducted with large numbers of patients to assess the reported treatment outcomes because evidence in Zambia has indicated that conventional doses of radical chemo-radiation are well tolerated and effective for HIV-seropositive women who are on HAART[116].

The effectiveness of chemotherapy alone on the survival of HIV-seropositive women with advanced cervical cancer (stage IVB) was found to be modest, with a median overall survival of about 13.2 months[119]. In addition, three radical hysterectomies (surgery) treatments on reasonably stable immunosuppressive HIV-seropositive patients with cervical cancer stage IB-IIA were found to produce good treatment and survival outcomes, with all three patients having negative vault cytologic smears after 3 and 6 years post-surgery[121]. However, because of the few patients reported in this radical hysterectomy study, there might be a need for a multi-centre study to explore further the impact of this treatment and associated outcomes. HIV-seropositive patients treated with other modalities such as surgery, radiation and chemo-radiation were shown to have an overall mortality of 324 per 1000 person-years, with 82% deaths as compared to 209 per 1000 person-years, with 93% among HIV-negative patients[120].

5.4 Young people and cervical cancer in an era of HIV

Resource constraints have limited the decentralisation and prioritisation of cervical cancer management in developing countries. In as much as Zimbabwe has undertaken cervical cancer screening, mostly for the 21-49 year age group, resource constraints have limited the decentralisation of cervical cancer cases, prioritisation of high-risk groups and cervical cancer awareness programmes. The current system of cervical cancer screening and management in Zimbabwe is based largely on secondary and tertiary health institutions and facilities. At the primary health care level, cervical cancer screening might first be offered at district hospitals

and city council polyclinics, with fragmented treatment only available at tertiary level. These challenges might be contributing to late diagnosis and high mortality rates reported to be over 69.0% (estimated 2000 cervical cancer deaths) annually[1,142].

On the other hand, recent years have witnessed an increase in risky lifestyle behaviour including early onset of sexual activity, multiple sexual partners and age-disparate relationships among the 15 to 24 year age group, resulting in high HIV incidence and placing young women at risk[67]. HIV incidence for young women between the ages of 15-24 years is reported to be twice higher as compared to young men of the same age-group in Zimbabwe[68]. In addition, this study has shown that there is insufficient knowledge about sexual reproductive health including cervical cancer among young people. Young people in Zimbabwe have a general idea about cervical cancer and the seriousness thereof, but they lack adequate knowledge of risk factors and information on where to access cervical cancer services. Having heard about cervical cancer and considering it to be serious does not necessarily correspond to young people having a correct understating of the disease and its associated risk factors. There were no significant differences on knowledge of cervical cancer and its risk factors between high school and university students or rural and urban students and this might indicate lack of cancer education or awareness at a national level. Similar results were found among a study that assessed women's knowledge, attitude and practices towards cervical cancer screening Zimbabwe[17].

The current cervical cancer screening strategies especially in Zimbabwe target women older than 21 years old[16] but this study has shown that the knowledge of the screening services and their availability is very low even among young people between the ages of 21 to 24 years. Generally, young people were unable to mention cervical cancer risk factors or know about cervical cancer screening and where it is offered. In addition, the synthesised evidence in this study suggests that those who are HIV-infected and have got cervical cancer, are relatively

young with average ages ranging from 35 to 40 years. Considering the long incubation period for someone to develop cervical cancer, it might be argued that targeting young people in cervical cancer prevention, by screening from the ages of 15 years, in light of HIV incidence among them, might be beneficial and cost-effective in the near future.

Zimbabwe does not have a cancer primary prevention strategy that focuses on cancer risk factors[16]. The HBM and SEM believe that increasing knowledge and awareness of a disease, in this case, cervical cancer, may play a role in improving health care seeking behaviour among young people towards cervical cancer prevention services. Based on the HBM and SEM, lack of information and knowledge about cervical cancer, especially as found in this study, are some of the reasons that contribute to underutilisation of screening services, late diagnosis of the condition, and a high mortality rate. Young people in this study (including the young men's perception towards their girlfriends and wives) did not feel susceptible to cervical cancer because of various reasons ranging from being faithful, to having being circumcised and not using detergents that are believed to cause cancer. This finding of lack of susceptibility towards cervical cancer by young people is almost similar to what was found in other studies among women[143,144]. In addition, there is a lack of cervical cancer prevention policies even in light of the newly launched Mass HPV Vaccination Programme for young girls in Zimbabwe. These legislation and policy challenges might be contributing to the fragmentation of cervical cancer service provision and failure to prevent 'silo' operation among different partners within the sexual reproductive health management space.

Lastly, Zimbabwe remains a patriarchal society and most men continue to make decisions on the health of women, from providing for money for hospital fees to deciding if it is necessary for women to seek medical attention. This study highlights the ignorance that young people, especially young men, have on cervical cancer and its screening. Men continue to be side-lined

in health prevention programmes and this has fuelled their passive nature towards health-seeking behaviour, as some responses from young men in this study have shown.

5.5 Study limitations

This study had several limitations. For the cross-sectional component, convenient sampling was used for university students and this made it difficult to generalise their sentiments for the whole country. In addition, those who participated in this study might have been different from those who could not participate because they were attending lectures or writing examinations. The research findings might have underestimated the extent of lack of knowledge, attitude and practices of young people towards cervical cancer due to the non-response rate of high school students. Therefore, these results require to be interpreted with caution and an understanding of the context that it took place.

For the two systematic reviews, the overall quality of evidence of the included studies, which was 'moderate', made it difficult to draw emphatic conclusions on which screening or treatment method is effective on HIV-seropositive women and which one is suitable for low-income countries. Validity of results was further decreased by the small numbers of participants in some of the included papers, risk of bias associated with the study designs, completeness of data and lack of explanations on the statistical analyses conducted. Lastly, by limiting the search to studies reported in English in the prevention review, some relevant studies published in other languages might have been missed.

CHAPTER SIX: IMPLICATIONS OF THE STUDY, CONCLUSIONS AND RECOMMENDATIONS

Note: Some of the conclusions in this chapter have been published in the BMC Systematic Reviews Journal (see Appendix 19).

6.1 Summary

Cervical cancer continues to be a major public health challenge in developing countries such as Zimbabwe where morbidity and mortality rates are high. This study has raised key questions about the state of cervical cancer control and management in a developing country looking at young people's knowledge, attitude and practices and prevention and treatment in HIV positive women. The research has shown that routine screening with a combination of Pap smear or VIAC and early treatment will prevent cases of cervical cancer by almost 80%. Moreover, the study has shown that young people who are associated with most of cervical cancer risk factors, have some idea about cervical cancer and have a positive attitude in wanting to learn more, but they lack an understanding on its risk factors and how it should be prevented.

This chapter links the evidence and conclusions to the aim of the study, which was to synthesise and document published evidence relating to the available cervical cancer screening and treatment modalities for HIV-seropositive women in developing countries. As well as to investigate the knowledge, attitudes and practices of young people (15 to 24 years old) in Zimbabwe towards cervical cancer, screening, HPV and vaccination. The motivation for conducting the study was to explore and identify potential strategies on how to improve cervical cancer screening and treatment among HIV-seropositive women in developing countries. In addition, this research assessed the knowledge, attitude and practice of young people towards cervical cancer, HPV, cervical cancer screening and HPV vaccination in Zimbabwe, viz disjuncture with the prevailing global policy approach.

6.2 Cervical cancer management for a developing country with high HIV burden

HIV-seropositive women are a high-risk group for developing cancer[42,145] and identifying the ideal cervical cancer screening method for them will go a long way in reducing premature mortality among them. Findings of this study indicate a need for further research, most randomised controlled trials, that allows adequate follow-up of screened HIV-seropositive women and provide evidence on which screening method is best to use, taking into account age (especially the young women who are HIV-infected); one visit vs. return visit schemes; primary screening then triage; opportunistic vs. organised screening; CD4+ counts; antiretroviral therapy and quality of life.

Sequential screening using HPV test and VIA or VILI has the potential to offer a better catch of at-risk HIV-positive women[95] when compared to the other available screening methods and this can be a solid foundation that developing countries can start to formulate their cervical cancer screening guidelines for HIV-seropositive women. However, as indicated before, there is a need for further research that will provide evidence on the best way of using this combination since it was reported that such as sequential screening did not improve sensitivity or specificity[92].

Secondly, with the introduction of mass HPV vaccination among school going young girls, there exist potential opportunities to offer the vaccine to young boys through the same school-based system and young women and middle-aged HIV-seropositive women in developing countries within well-established HIV programmes. With HPV vaccine offering more than 12 months protection in HIV-seropositive women[146], this might be a cost-effective and simple method to offer cervical cancer prevention among these women. In addition, HPV vaccination will offer a solution to the lack of adequate suitable infrastructure and trained professionals that have hampered Pap smear screening in developing countries.

Developing countries should strive to offer both opportunistic and organised coordinated screening programmes in the form of provider-initiated services. Furthermore, there is a need to expand the integration of provider-initiated cervical cancer screening services in already existing HIV services so as to enable early detection and treatment and offer a 'one-stop' shop. Developing countries can think of individualising cervical cancer screening depending on their available resources and context to cater for the benefit of different screening methods and the general health status of the HIV-seropositive women. This is in light with the proposed see-see-and treat method (see Figure 5.1) where the potential of high false positives and over treating can be reduced significantly[103].

Majority of cervical cancer patients are reported to be diagnosed at an advanced stage of the disease because of lack of knowledge, awareness and coordinated and systematic screening[42,147]. In addition, lack of optimal treatment regimen due to factors such as lack of infrastructure, financial, and human resources have been found to contribute to poor outcomes of treatment among HIV-seropositive women in developing countries[147-148]. The findings of this study have shown that the available cervical cancer treatments, radiotherapy, chemotherapy, chemo-radiation and surgery are effective for HIV-seropositive patients and are the same treatments being used for HIV-negative patients. This systematic review has also suggested that cervical cancer stage, immunosuppressive level, and multisystem toxicities due to treatment are associated with treatment completion, prognostic and survival outcomes[115-117]. Radiotherapy has been found to be more associated with most acute skin, gastrointestinal and genitourinary tract toxicities and suggestions of palliative fractionation to relatively stable patients to improve response and treatment completion require further multicentre studies. Those infected with HIV were of a younger age and advanced disease as compared to those who were HIV-negative[110-120]. This finding point to the need to expand cervical cancer prevention strategies to target young people who were found to lack knowledge on the risk

factors of the disease. In as much as the mass HPV vaccination is targeting 9 to 14 year old young girls, it can be argued, based on the findings from this study, that it might be ideal to reduce the age of cervical cancer screening from the recommended 21 years and above to include those from 15 years, especially those who are HIV-infected. This might help in early identification and capturing of high-risk young people who lack knowledge about cervical cancer risk factors. Facilitation and putting HIV-infected people on life-long ART is of importance and has been found to have a positive impact on cervical cancer treatment response.

6.3 Advocating for an inclusive cervical cancer policy in Zimbabwe

The National Cancer Prevention And Control Strategy For Zimbabwe 2013 – 2017, which encompassed cervical cancer prevention and management, was not fully implemented due to the inadequacy of cancer legislation and resource constraints. This has contributed to continued fragmentation of service provision. Despite the introduction of the Mass HPV Vaccination Programme in May 2018, the country lacks policy guidance on how such initiatives will be sustained and made available to meet the Ministry of Health and Child Care's mission of providing equitable access to quality health care to everyone. With the introduction of the Mass HPV Vaccination programme for young girls, is it an opportune time for Zimbabwe to introduce an inclusive cervical cancer policy?

In 2009, WHO advocated for a coordinated strategy towards the prevention of cervical cancer since the sexual behaviour of both men and women is a major risk factor for cervical cancer[147]. Involving men in cervical cancer prevention strategies is key to reinforcing the drive to enhance the disease's management and this also has a cost-benefit relationship[149]. Zimbabwe can develop and ring-fence her cervical cancer prevention and management plans by developing a policy in line with WHO coordinated strategy. The policy might need to incorporate primary and community cervical cancer prevention and management initiatives, pool together all public

and private cervical cancer providers and support a financing system that can provide access to affordable, quality cervical cancer services.

6.4 Analytic frameworks that might help decision-making in cervical cancer prevention in developing countries

For developing countries, questions on how to implement and sustain cervical cancer screening in light of limited resources (human and financial), inadequate infrastructure and lack of screening programmes, still exist. The questions continue to have an impact on decision-making towards screening and even prioritisation of HIV-seropositive women. In as much as this review has generated synthesised evidence on cervical cancer screening and treatment of HIV-seropositive women and young people's knowledge, attitude and practices towards cervical cancer, utilisation and implementation of some of this evidence will need to be context specific. A number of analytic frameworks for decision-making in cervical cancer prevention and management exists[150-153] and these frameworks may help developing countries in identifying cost-effective strategies towards screening and treatment of HIV-seropositive women as well as develop cervical cancer primary prevention strategies that encompass young people. These analytic frameworks can assist developing countries to make decisions after considering the provided evidence, epidemiological factors, political and economic factors, and issues around equity and costumers' preferences[154]. Such a transparent and systematic way of making decisions has been shown to have a positive impact on reducing cervical cancer burden[151,153].

6.5 Implications of this study to evidence-based health care

Based on the proposed opportunities for prevention of cervical cancer in HIV-seropositive women (see Figure 5.1), a number of key messages around the reliability of the found evidence are beginning to emerge:

- There is no best available cervical cancer screening method/tool for HIV-seropositive women and the generated evidence by this study can be effective in certain contexts but not all. Future research can explore the feasibility, appropriateness, meaningfulness and cost-effectiveness of the HPV vaccine, use of the see-see-and-treat using VIA/VILI, colposcopy and cryotherapy, and sequential screening using VIA/VILI and or HPV testing in HIV burdened countries. Whatever method is to be used, the invention of a systematic screening approach, which could be helpful, should be investigated and based on cervical cancer analytic frameworks to allow transparent and systematic decision-making.
- Clients or patients should at least have an option to decide on which screening method they would prefer based on the risk-benefit balance and this should be guided by the professional judgement of health care staff.
- Both cervical neoplasia and cervical cancer in HIV-seropositive women are treatable with the available treatment. There is a need for good clinical management of HIV-seropositive women undergoing chemo-radiation to manage multisystem toxicities that have a bearing on treatment completion, prognostic and survival outcomes. Research on cervical cancer management of HIV-seropositive patients focusing on the quality of life of those treated, the effectiveness of the treatment method taking into account CD4+ count and ART is required.
- Most HIV-seropositive women with cervical cancer are of young age and screening from the age of 15 years, taking into consideration early sexual debut, lack of cervical cancer knowledge among the young and high HIV incidence, might increase early identification of at-risk young women. Multicentre research on early screening of young women is required to inform feasibility, appropriateness, meaningfulness and cost-effectiveness.

6.6 Recommendations

With the government of Zimbabwe having responded positively to the global call for introducing mass HPV vaccination among young girls, which they started in May 2018, there might be a need for the government to support this initiative with a sound national policy and strategic framework.

Recommendation 1: Government of Zimbabwe should show political will in the fight to reduce morbidity and mortality of cervical cancer through providing a budget towards the recently launched National HPV Vaccination Programme. This budget should be ring-fenced as was done in other countries like South Africa as a way of offering a solid financial base for this vaccination drive.

Recommendation 2: Government should strengthen cervical cancer prevention by investing in a communication strategy as a primary prevention tool to deliver awareness and education at a population- and community-level. The communication strategy should be evidence-informed to promote learning, awareness and equipping young people to make informed decisions about their sexual and reproductive health.

Recommendation 3: The communication strategy may be integrated into the formal education system for it to run concurrently with the school-based mass HPV vaccination drive. Behaviour change messages around cervical cancer risk factors can be disseminated through social media platforms as a way of communicating consistent messages to a broader audience and increase the knowledge and attitudes of young people.

Recommendation 4: Healthcare workers are critical in health promotion and education and should be adequately trained and skilled in all aspects of cervical cancer prevention and treatment. Healthcare workers' knowledge and curricula at training institutes and healthcare facilities should be updated and aligned with new evidence to be relevant.

Recommendation 5: In a culturally sensitive society as Zimbabwe, vaccinating every young girl will not be easy. The government should design an inclusive cervical cancer policy that will equip and improve both the young person, their families and community in shared decision making around sexual and reproductive health. There is a need for the government to pay attention to how far young people control their own sexual and reproductive health and how much a family or society shape those decisions. The inclusive policy should provide a framework that promotes open discussions towards cervical cancer prevention and how men (both young and old) contribute to cervical cancer prevention. This policy should also allow for social mobilisation towards the National HPV Vaccination Programme and this is a critical aspect that has helped South Africa record successes in vaccinating many young girls between 2014 and 2016.

Recommendation 6: Monitoring and evaluation of national programmes have proved to be a challenge in most low- and middle-income countries and this has resulted in countries planning and allocating resources based on inaccurate and poor data. The National HPV Vaccination Programme should be regularly adapted and updated to ensure quality controls and implementation and this may be achieved through ongoing monitoring and evaluation of the vaccine's uptake and schools that might have been missed, reported side-effects and their management, the vaccination coverage and vaccine-stock management.

Recommendation 7: With a high heterosexual transmission of HIV and high HIV prevalence, consideration for HPV vaccination of young men and HIV-positive women up to the age of 25 years may be vital in the drive to reach saturation quickly, reduce cervical cancer and other HPV-associated diseases.

References

1. Zimbabwe National Cancer Registry. Cervical Cancer: the leading cancer in Zimbabwe 2010. [Accessed on the 13th of November, 2013 from] http://www.cancerassociation.co.zw/cervical-cancer-leading-cancer-zimbabwe
2. Chirenje Z.M. HIV and cancer of the cervix. Best Pract Res Clin Obstet Gynaecol 2005; 19: 269-276
3. Maiman M, Fruchter RG, Clark M, Arrastia CD, Matthews R, Gates EJ. Cervical cancer as an AIDS-defining illness. Obstet Gynecol 1997, 89: 76–80
4. Barnes A, Betts AC, Borton, Eric K, Sanders JM, Pruitt SL, Werner C, Bran A, Estelle CD, Balasubramanian BA, Inrig SJ, Halm EA, Skinner CS, Tiro JA. Cervical cancer screening among HIV-infected women in an urban, United States safety-net healthcare system. AIDS 2018; 32(13): 1861–1870
5. Gerressu M, Stephenson JM. Sexual behaviour in young people. Curr Opin Infect Dis, 2008;21(1):37-41.
6. Glanz K. Rimer BK. Lewis FM. Health behaviour and Health education. Theory, Research and Practice 2002. San Francisco. Wiley and Sons
7. Conmar M. Norman P. Predicting health behaviour. Search and practice with social cognition models. Open University Press 1996. Ballmore. Buckingham
8. World Health Organisation. Cervical cancer, human papillomavirus (HPV), and HPV vaccines: Key points for policy-makers and health professionals. Geneva 2007
9. World Health Organisation. Human Papillomavirus (HPV). Available at http://www.who.int/immunization/topics/hpv/en/
10. Parkin D.M. Ferlay J. Hamdi-Cherif M, et al. Cervix Cancer in Africa: epidemiology and prevention. Lyon, France: IARC Press, 2003: 268–276.

11. Wabinga H.R. Parkin D.M. Wabwire-Mangen F. Nambooze S. Trends in cancer incidence in Kyadondo County, Uganda, 1960–1997. British Journal for Cancer 2000; 82: 1585–1592.

12. Chirenje ZM, Rusakaniko S, Kirumbi L, Ngwalle EW, Makuta-Tlebere PP, Kaggwa S, Mpanju-Shumbusho W, Makoae L. Situation analysis for cervical cancer diagnosis and treatment in East, Central and Southern African countries. World Health Organisation, 2001; 79(2): 127-132

13. Ghebre RG, Grover S, Xu MJ, Chuang LT, Simonds H. Cervical cancer control in HIV-infected women: Past, present and future. Gynecologic Oncology Reports, 2017; 21: 101-108

14. Soerjomataram I, Lortet-Tieulent J, Parkin DM et al. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. Lancet. 2012;380(9856): 1840-50

15. Ferlay J, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International Journal for Cancer 2010; 127: 2893–2917.

16. Kuguyo O, Matimba A, Tsikai N, et al. Cervical cancer in Zimbabwe: a situation analysis. Pan Afr Med J. 2017;27:215.

17. Mupepi, S.C. Sampselle, C.M. and Johnson, T.R.B. Knowledge, attitudes, and demographic factors influencing cervical cancer screening behaviour of Zimbabwean women. Journal of Women's Health 2011; 20(6): 943-952

18. Marlow, L., Waller, J., Evans, R., Wardle, J. Predictors of interest in HPV vaccination: A study of British adolescents. Vaccine 2009; 27(18): 2483-2488.

19. Tavafian SS. Predictors of cervical cancer screening: an application of the Health Belief Model. Tarbiat Modares University 2012, Iran.

20. Simons-Morton, B., K. R. McLeroy, and M. L. Wendel. 2012. Behavior theory in health promotion practice and research. Burlington, MA: Jones & Bartlett Learning.

21. Eubanks V. Breast and Cervical Cancer Control Program (BCCCP) and Well-Integrated Screening and Evaluation for Women across the Nation (WISEWOMAN): Improving health outcomes. University of North Carolina, 2012.

22. Centers for Disease Control and Prevention. Increasing population-based breast and cervical cancer screening. An Action Guide to Facilitate Evidence-based Strategies. US Department of Health and Human Sciences, 2014.

23. American Cancer Society. What is cervical cancer? [Accessed on the 21st of May 2014 from] http://www.cancer.org/cancer/cervicalcancer/detailedguide/cervical-cancer-what-is-cervical-cancer

24. World Health Organisation position paper: Human papillomavirus vaccines. Geneva 2009. 118-131 http://www.who.int/immunization/newsroom/recommendation_HPV_vaccination/en/index_html

25. de Sanjose S, Quint WG, Alemany L, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010;11(11): 1048-56

26. Zhu H, Shen Z, Luo H, Zhang W, Zhu X. Chlamydia Trachomatis Infection-Associated Risk of Cervical Cancer: A Meta-Analysis. Medicine (Baltimore), 2016;95(13):e3077.

27. Demarteau N. Breuer T. Standaert B. Selecting a mix of prevention strategies against cervical cancer for maximum efficiency with an optimization program. Pharmacoeconomics 2012; 30: 337-353

28. McFadden S.E. Schumann L. The role of human papillomavirus in screening for cervical cancer. Journal Am Acad Nurse Practice 2001; 13: 116-125

29. Shields T.S. Brinton L.A. Burk R.D, et al. A case-control study of risk factors for invasive cervical cancer among U.S women exposed to oncogenic types of human papillomavirus. Cancer Epidemiology Biomakers Prevention 2004; 13: 1574-1582

30. Molijn A. Kleter B. Quint Q. van Doorn LJ. Molecular diagnosis of human papillomavirus (HPV) infections. Journal of Clinical Virology 2005; 32S: S43-S51

31. Bosch F.X. Lorincz A. Munoz N, et al. The causal relation between human papillomavirus and cervical cancer. Journal of Clinical Pathology 2002; 55: 244-265

32. Palefsky J.M. Holly E.A. Molecular virology and epidemiology of human papillomavirus and cervical cancer. Cancer Epidemiology Biomarkers Prevent 1998; 4: 425-428

33. Muñoz N, Bosch FX, de Sanjosé S, et al. The causal link between human papilloma- virus and invasive cervical cancer: a population-based case-control study in Colombia and Spain. Int J Cancer 1992; 52: 743-749.

34. Walboomers JMM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer world- wide. J Pathol 1999; 189: 12-19.

35. Muñoz N, Bosch FX, de Sanjosé S, et al. Epidemiologic Classification of Human Papillomavirus Types Associated with Cervical Cancer. N Engl J Med 2003; 348: 518-527.

36. Odendal L. Cervical cancer in women with HIV. HIV & AIDS Treatment in Practice 2011; 174. HATiP. www.aidsmap.com

37. Melnikow J et al. Natural history of cervical squamous intraepithelial lesions: A meta-analysis. Obstet Gynecol 1998; 92: 727-735

38. Hogewoning CJA et al. Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papilloma virus: a randomised clinical trial. Int J Cancer 2000; 107: 811-816.

39. Mishra GA, Pimple SA, Shastri SS. An overview of prevention and early detection of cervical cancers. Indian J Med Paediatr Oncol. 2011;32(3): 125-32

40. Fallala MS, Mash R. Cervical cancer screening: safety, acceptability and feasibility of a single-visit approach in Bulawayo, Zimbabwe. Afr J Prm Health Care Fam Med. 2015; 7(1): 742-9

41. Cancers of the female reproductive organs. In: Stewart B, Wild C, editors. World cancer report 2014 Lyon: International Agency for Research on Cancer; 2014. p. 465

42. Santesso N, Mustafa RA, Schünemann HJ, Arbyn M, Blumenthal PD, Cain J, Chirenje M et al. World Health Organization Guidelines for treatment of cervical intraepithelial neoplasia 2-3 and screen-and-treat strategies to prevent cervical cancer. Int J Gynaecol Obstet, 2016; 132(2): 252-258

43. National Cancer Institute. Health NIo. Cervical Cancer. 2014

44. Sankaranarayanan R, Anorlu R, Sangwa-Lugoma G, Denny LA. Infrastructure requirements for human papillomavirus vaccination and cervical cancer screening in sub-Saharan Africa. Vaccine. 2013; 31 (Suppl 5): F47-52

45. Uberti-Foppa C, Origoni M, Maillard M, Ferrari D, Ciuffreda D, Mastrorilli E, Lazzarin A, Lillo F. Evaluation of the detection of human papillomavirus genotypes in cervical specimens by hybrid capture as screening for precancerous lesions in HIV-positive women. Journal of medical virology, 1998; 56(2):133–137

46. World Health Organization. Global Health Observatory Data Repository: Number of people (all ages) living with HIV. Switzerland: 2014

47. Mabeya H, Khozaim K, Liu T, Orango O, Chumba D, Pisharodi L, Carter J, Cu-Uvin S. Comparison of conventional cervical cytology versus visual inspection with acetic acid among human immunodeficiency virus-infected women in Western Kenya. Journal of lower genital tract disease, 2012; 16(2):92–97.

48. World Health Organization. WHO Guidelines: WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. Geneva, Switzerland: World Health Organization; 2013

49. Elit L, Fyles AW, Devries MC, et al. Follow-up for women after treatment for cervical cancer: a systematic review. Gynecol Oncol 2009; 114:528.

50. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology. Available at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

51. Chung LT, Temin S, Berek JS. Management and care of women with invasive cervical cancer: American Society of Clinical Oncology resource-stratified clinical practice guideline summary. J Oncol Pract, 2016;12(7): 693-696

52. Chung and Koh WJ, Greer BE, Abu-Rustum NR, Apte SM, Campos SM, Cho KR et al. Cervical cancer, version 2.2015. J Natl Compr Cancer Netw, 2015; 13(4): 404

53. Connor S, Bermedo M. Global atlas of palliative care at the end of life, 2014

54. Fletcher FE, Vidrine DJ, Tami-Maury I, Danysh HE, King RM, Buchberg M, Arduino RC, Gritz ER. Cervical Cancer Screening Adherence among HIV-Positive Female Smokers from a Comprehensive HIV Clinic. AIDS Behav. 2014; 18(3): 544–554

55. Sherris J. Herdman C. Elias C. Cervical cancer in the developing world. West J Med. 2001; 175(4): 231–233.

56. World Health Organisation, Reproductive Health, World Health Organisation. Chronic diseases, health promotion. In: Comprehensive cervical cancer control: A guide to essential practice, 2nd ed 2014. World Health Organisation

57. Clifford GM, Polesel J and Rickenbach M Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. Journal of the National Cancer Institute, 2005; 97 (6).

58. Moodley JR. Hoffman M. Carrara H. Allan BR. Cooper DD. Rosenberg L et al. HIV and pre-neoplastic and neoplastic lesions of the cervix in South Africa: a case-control study. BMC Cancer, 2006; 6:135

59. Kojic EM, Rana AI, Cu-Uvin S. Human Papillomavirus Vaccination in HIV-infected Women: Need for Increased Coverage. Expert review of vaccines. 2016;15(1):105-117

60. Chokunonga E, Borok MZ, Chirenje ZM, Makunike-Mutasa R, Ndlovu N, Nyakabau AM, Vuma S. Zimbabwe National Cancer registry: 2014 Annual Report: pattern of cancer in Zimbabwe. Accessed on 5 April 2017.

61. Information Centre for Cancer. Human papillomavirus in Zimbabwe report.

62. Tota, J.E. Ramana-Kumar, A.V. El-Khatib, Z. Franco, E.L. The road ahead for cervical cancer prevention and control. Current Oncology 2014; 21(2)

63. The World Bank. Annual Report 2014. [Accessed on the 10th of January 2015 from worldbank.org/annualreport2014]

64. Kharsany AB, Karim QA. HIV infection and AIDS in sub-Saharan Africa: current status, challenges and opportunities. Open AIDS J. 2016;10:34–48

65. Schaefer R, Gregson S, Eaton J, Mugurungi O, Rhead R, Takaruza A, Maswera R, Nyamukapa C. Age-disparate relationships and HIV incidence in

adolescent girls and young women: evidence from Zimbabwe. AIDS Issue, 2017; 31(10): 1461–1470

66. Shisana O, Rehle T, Simbayi LC, Zuma K, Jooste S, Zungu N, et al. South African national HIV prevalence, incidence and behaviour survey, 2012. Cape Town, South Africa: Human Sciences Research Council, South Africa; 2014.

67. Zimbabwe National Statistics Agency (2016) 'Zimbabwe Demographic and Health Survey 2015'

68. Zimbabwe National Statistics Agency (2015) 'Zimbabwe Demographic and Health Survey 2015: Key Indicators'.39-40

69. Taira AV, Neukermans CP, Sanders GD. Evaluating human papillomavirus vaccination programs. Journal of Emerging Infectious Diseases 2004; 10(11): 1915-1923

70. Perlman, S. Wamai, R.G. Bain, P.A. Welty, T. Welty, E. Ogembo, J. G. Knowledge and awareness of HPV vaccine and acceptability to vaccinate in Sub-Saharan Africa: A systematic review. PLoS One 2014; 9(3)

71. Francis SA. Nelson J. Liverpool J. Soogan S. Mofammere N. Thorpe Jr RJ. Examining attitudes and knowledge about HPV and cervical cancer risk among female clinic attendees in Johannesburg, South Africa. Vaccine 2010; 28: 8026–8032.

72. Francis SA. Battle-Fisher M. Liverpool J. Hipple L. Mosavel M. Soogan S et al. A qualitative analysis of South African women's knowledge, attitudes, and beliefs about HPV and cervical cancer prevention, vaccine awareness and acceptance, and maternal child communication about sexual health.

73. Mollers, M. Lubbers, K. Spoelstra, S.K. Weijmar-Schultz, W.C.M. Daemen, T. Westra, T.A. van der Sande, M.A.B. Nijman, H.M. de Melkar, H.E. Tami, A. Equity in human papilloma virus vaccination uptake?: Sexual behaviour, knowledge and demographics in a cross-sectional study in (un)vaccinated girls in the Netherlands. BMC Public Health 2014; 14: 288

74. Liddon N, Pulley L, Cockerham WC, et al. Parents'/ guardians' willingness to vaccinate their children against genital herpes. Journal of Adolescent Health, 2005; 37: 187-193.

75. Marais DJ. Constant D. Allan B. Carrara H. Hoffman M. Shapiro A. et al. Cervical human papillomavirus (HPV) infection and HPV type 16 antibodies in South African Women. Journal of Clinical Microbiology 2008; 46(2): 732-739

76. Moher D. Liberati A. Tetzlaff J. Altman D.G. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7)

77. PROSPERO. http://www.crd.york.ac.uk/Prospero/

78. United Nations. Country classification. World Economic Situation and Prospects 2012. http://www.un.org/en/development/desa/policy/wesp/wesp_current/2012country_class.pdf

79. LaMorte W.W. Follow Up in Cohort Studies. Boston University School of Public Health, 2016. http://sphweb.bumc.bu.edu/otlt/MPH-Modules/EP/EP713_CohortStudies/EP713_CohortStudies4.html

80. Slavin R.E and Smith D. Effects of sample size on effect size in systematic reviews in Education. Society for Research and Effective Education, Crystal City, Virginia, March 3-4, 2008

81. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Quality Assessment Scale. Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 11 Oct 2016]

82. NIH Study Quality Assessment Tools. Available at https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools [Accessed 2 October 2017]

83. Vittinghoff E, Glidden DV, Shiboski SC, McCulloch CE (2004) Regression methods in biostatistics - Linear, logistic, survival, and repeated measures models. Springer-Verlag. (Chapter 5.5.3.): 340

84. Mapanga W, Elhakeem A, Feresu SA, Maseko F, Chipato T. Prevention of cervical cancer in HIV-seropositive women from developing countries: a systematic review protocol. Syst Rev, 2017; 6(1):91. -017-0484-9

85. Huchko MJ, Sneden J, Zakaras, JM, Smith-McCune K, Sawaya G, Maloba M, Bukusi E, et al. A randomized trial comparing the diagnostic accuracy of visual inspection with acetic acid to visual inspection with Lugol's iodine for cervical cancer screening in HIV-infected women. Plos One, 2015. DOI:10.1371/journal.pone.0118568

86. Kuhn L, Wang C, Tsai WY, Wright TC, Denny L. Efficacy of human papillomavirus-based screen-and-treat for cervical cancer prevention among HIV-infected women. AIDS, 2010; 24(16):2553–2561.

87. Huchko MJ, Sneden J, Leslie HH, Abdulrahim N, Maloba M, Bukusi E, et al. A comparison of two visual inspection methods for cervical cancer screening among HIV-infected women in Kenya. Bulletin of the World Health Organization, 2014; 92(3):195-203.

88. Obiri-Yeboah D, Adu-Sarkodie Y, Djigma F, Akakpo K, Aniakwa-Bonsu E, Amoako-Sakyi D, et al. Options in human papillomavirus (HPV) detection for cervical cancer screening: comparison between full genotyping and a rapid qualitative HPV-DNA assay in Ghana. Gynecol Oncol Res Pract, 2017; 4:5.

89. Obiri-Yeboah D, Adu-Sarkodie Y, Djigma F, Hayfron-Benjamin A, Abdul L, Simpore J, et al. Self-collected vaginal sampling for the detection of genital human papillomavirus (HPV) using careHPV among Ghanaian women. BMC Women's Health, 2017; 17(1):86.

90. Bansil P, Lim J, Byamugisha J, Kumakech E, Nakisige C, Jeronimo JA. Performance of Cervical Cancer Screening Techniques in HIV-Infected Women in Uganda. J Low Genit Tract Dis, 2015; 19(3):215-9.

91. Cholli P, Bradford L, Manga S, Nulah K, Kiyang E, Manjuh F, et al. Screening for cervical cancer among HIV-positive and HIV-negative women in Cameroon using simultaneous co-testing with careHPV DNA testing and visual inspection enhanced by digital cervicography: Findings of initial screening and one-year follow-up. Gynecol Oncol, 2018; 148(1):118-25.

92. Chung MH, McKenzie K, De Vuyst H, et al. Comparing Papanicolaou smear, visual inspection with acetic acid and human papillomavirus cervical cancer screening methods among HIV-positive women by immune status and antiretroviral therapy. AIDS, 2013; 27(18): 2909–2919.

93. Dartell MA, Rasch V, Ifner T, et al. Performance of visual inspection with acetic acid and human papillomavirus testing for detection of high-grade cervical lesions in HIV positive and HIV negative Tanzanian women. Int J Cancer, 2014; 135(4):896–904.

94. Firnhaber C, Goeieman B, Faesen M, Levin S, Williams S, Rameotshela S, et al. Prospective One Year Follow Up of HIV Infected Women Screened for Cervical Cancer Using Visual Inspection with Acetic Acid, Cytology and Human Papillomavirus Testing in Johannesburg South Africa. PLoS One, 2016; 11(1):e0144905.

95. Joshi S, Sankaranarayanan R, Muwonge R, Kulkarni V, Somanathan T, Divate U. Screening of cervical neoplasia in HIV-infected women in India. AIDS, 2013; 27(4):607-15.

96. Lim K, Davidson A, Harwell J, Thay S, Boardman LA, Feller E, et al. Comparing Visual Inspection with Acetic Acid to Cytology in Detection of Precancerous Lesions of the Cervix in HIV-Infected Cambodian Women. J Int Assoc Physicians AIDS Care (Chic), 2011;10(5):283-6

97. Mabeya H, Khozaim K, Liu T, et al. Comparison of conventional cervical cytology versus visual inspection with acetic acid (VIA) among HIV-infected women in western Kenya. J Low Gen Tract Dis, 2012;16(2):92–97

98. Michelow P, Sherrin A, Rossouw L, Mohaleamolla S, Evans D, Swarts A, et al. Performance of the Cellslide((R)) automated liquid-based cytology system amongst HIV-positive women. Afr J Lab Med, 2016;5(1):278

99. Sahasrabuddhe VV, Bhosale RA, Kavatkar AN, Nagwanshi CA, Joshi SN, Jenkins CA, et al. Comparison of visual inspection with acetic acid and cervical cytology to detect high-grade cervical neoplasia among HIV-infected women in India. Int J Cancer, 2012; 130(1):234-40.

100. Akinwuntwan L, Adesina OA, Okolo CA, et al. Correlation of cervical cytology and visual inspection with acetic acid in HIV-positive women. J Obstet and Gynaecol, 2008; 28(6):638–641.

101. Segondy M, Kelly H, Djima F, et al. Performance of careHPV for detecting high-grade cervical intraepithelial neoplasia among women living with HIV-1 in Burkina Faso and South Africa: HARP study. Br J Cancer, 2016; 115(4):425–430.

102. Bateman AC, Parham GP, Sahasrabuddhe VV, Mwanahamuntu MH, Kapambwe S, Katundu K, et al. Clinical performance of digital cervicography and

cytology for cervical cancer screening in HIV-infected women in Lusaka, Zambia. J Acquir Immune Defic Syndr, 2014; 67(2): 212-215

103. Mutyaba T, Mirembe F, Sandin S, Weiderpass E. Evaluation of 'see-see and treat' strategy and role of HIV on cervical cancer prevention in Uganda. Reprod Health, 2010; 7:4.

104. Ngou J, Gilham C, Omar T, Goumbri-Lompo O, Doutre S, Michelow P, et al. Comparison of analytical and clinical performances of the digene HC2 HPV DNA assay and the INNO-LiPA HPV genotyping assay for detecting high-risk HPV infection and cervical neoplasia among HIV-positive African women. J Acquir Immune Defic Syndr, 2015; 68(2):162-8.

105. Ngou J, Magooa MP, Gilham C, Djigma F, Didelot MN, Kelly H, et al. Comparison of careHPV and hybrid capture 2 assays for detection of high-risk human Papillomavirus DNA in cervical samples from HIV-1-infected African women. J Clin Microbiol, 2013; 51(12):4240-2.

106. Firnhaber C, Mayisela N, Mao L, et al. Validation of cervical cancer screening methods in HIV positive women from Johannesburg South Africa. PLoS One, 2013; 8(1):e53494.

107. Wu TJ, Smith-McCune K, Reuschenbach M, von Knebel Doeberitz M, Maloba M, Huchko MJ. Performance of p16INK4a ELISA as a primary cervical cancer screening test among a large cohort of HIV-infected women in western Kenya: a 2-year cross-sectional study. BMJ Open, 2016; 6(9): e012547.

108. Chibwesha CJ, Frett B, Katundu K, et al. Clinical performance validation of 4 point-of-care cervical cancer screening tests in HIV-infected women in Zambia. J Low Gen Tract Dis, 2016; 20(3): 218–223.

109. Adamson PC, Huchko MJ, Moss AM, Kinkel HF, Medina-Marino A. Acceptability and accuracy of cervical cancer screening using a self-collected tampon for HPV messenger-RNA testing among HIV-infected women in South Africa. PLoS One, 2015; 10(9): e0137299.

110. Woo VG, Cohen CR, Bukusi EA, Huchko M. Loop Electrosurgical Excision Procedure: Safety and Tolerability Among Human Immunodeficiency Virus-Positive Kenyan Women. Obstet Gynecol, 2011; 118(3): 554–559

111. Kietpeerakool C, Srisomboon J, Suprasert P, Phongnarisorn C, Charoenkwan K, Cheewakriangkrai C, Siriaree S, Tantipalakorn C, Pantusart A. Outcomes of loop electrosurgical excision procedure for cervical neoplasia in human immunodeficiency virus–infected women. Int J Gynecol Cancer 2006; 16: 1082–1088

112. Kietpeerakool C, Suprasert P, Srisomboon J. Outcomes of loop electrosurgical excision procedure for HIV-positive women in a low-resource outpatient setting. International Journal of Gynecology and Obstetrics 2009; 105: 10-13

113. Firnhaber C, Swarts A, Goeieman B, Rakhombe N, Mulongo M, Williamson AL, Michelow P, Ramotshela S, Faesen M, Levin S, Wilkin T. Cryotherapy Reduces Progression of Cervical Intraepithelial Neoplasia Grade 1 in South African HIV-Infected Women: A Randomized, Controlled Trial. J Acquir Immune Defic Syndr 2017;76:532–538

114. Smith JS, Sanusi B, Swarts A, Faesen M, Levin S, Goeieman B, Ramotshela S, Rakhombe N, Williamson AL, Michelow P, Omar T, Hudgens MG, Firnhaber C. A randomized clinical trial comparing cervical dysplasia treatment with cryotherapy vs loop electrosurgical excision procedure in HIV-seropositive women from Johannesburg, South Africa. Am J Obstet Gynecol 2017; 217:183.e1-11

115. Simonds HM, Wright JD, du Toit N, Neugut AI, Jacobson JS. Completion of and early response to chemoradiation among HIV-positive and HIV-negative patients with locally advanced cervical carcinoma in South Africa. Cancer 2012; 118(11): 2971-2979

116. Mdletshea S, Munkupab H, Lishimpib K. Acute toxicity in cervical cancer HIV-positive vs. HIV-negative patients treated by radical chemo-radiation in Zambia. South Afr J Gynaecol Oncol 2016; 8(2): 37-41

117. Shrivastava SK, Engineer R, Rajadhyaksha S, Dinshaw KA. HIV infection and invasive cervical cancers, treatment with radiation therapy: toxicity and outcome. Radiother Oncol, 2005;74(1):31-5.

118. Gichangi P1, Bwayo J, Estambale B, Rogo K, Njuguna E, Ojwang S, Temmerman M. HIV impact on acute morbidity and pelvic tumor control following radiotherapy for cervical cancer. Gynecol Oncol, 2006;100(2):405-11

119. Boupaijit K and Suprasert P. Survival Outcomes of Advanced and Recurrent Cervical Cancer Patients Treated with Chemotherapy: Experience of Northern Tertiary Care Hospital in Thailand. Asian Pac J Cancer Prev 2016; 17(3): 1123-1127

120. Ferreira MP, Coghill AE, Chaves CB, Bergmann A, Thuler LC, Soares EA, Pfeiffer RM, Engels EZ, Soares MA. Outcomes of cervical cancer among HIV-infected and uninfected women treated at the Brazilian National Institute of Cancer (2001-2013). AIDS, 2017; 31(4): 523-531

121. Moodley M. Radical hysterectomy for cervical cancer amongst women infected with the human immunodeficiency virus. Int J Gynecol Cancer 2007; 17: 1264–1265

122. Viviano M, DeBeaudrap P, Tebeu PM, Fouogue JT, Vassilakos P, Petignat P. A review of screening strategies for cervical cancer in human immunodeficiency virus-

positive women in sub-Saharan Africa. International Journal of Women's Health, 2017; 9: 69-79

123. Shiferaw N, Salvador-Davila G, Kassahun K, et al. The single-visit approach as a cervical cancer prevention strategy among women with HIV in Ethiopia. Successes and lessons learned. Glob Health Sci Pract, 2016; 4(1): 87–98.

124. Crosbie EJ, Einstein MH, Franceschi S, Kitchener HC. Human papillomavirus and cervical cancer. Lancet, 2013; 382(9895): 889–899.

125. Schiffman, M.; Solomon, D. Cervical-cancer screening with human papillomavirus and cytologic cotesting. N. Engl. J. Med. 2013;369:2324–2331.

126. Alizon S, Murall CL, Bravo IG. Why Human Papillomavirus Acute Infections Matter. Viruses. 2017; 9 (293); doi:10.3390/v9100293

127. Castle PE, Rodriguez AC, Burk RD, Herrero R, Wacholder S, Hildesheim A, et al. Long-Term Persistence of Prevalently Detected Human Papillomavirus Infections in the Absence of Detectable Cervical Precancer and Cancer. J Infect Dis. 2011; 203(6): 814–822.

128. Gravitt PE, Rositch AF. HPV self-testing and cervical cancer screening coverage. Lancet Oncol, 2014; 15(2): 128–129.

129. Palefsky J, Poongulali S, Lensing SY, Lee JY, Da Costa M, Jeeva A, Iqbal S, Kumarsami N. AMC 054: safety and Immunogenicity of the Quadrivalent HPV Vaccine in Indian HIV-Infected Women. Conference on Retroviruses and Opportunistic Infections, 2014; Boston, MA. 2014.

130. Kojic EM, Kang M, Cespedes MS, Umbleja T, Godfrey C, Allen RT, Firnhaber C, Grinsztejn B, Palefsky JM, Webster-Cyriaque JY, et al. Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. Clin Infect Dis, 2014; 59(1): 127–135.

131. Denny L, Hendricks B, Gordon C, Thomas F, Hezareh M, Dobbelaere K, Durand C, Herve C, Descamps D. Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine in HIV-positive women in South Africa: a partially-blind randomised placebo-controlled study. Vaccine, 2013; 31(48): 5745–5753.

132. Kahn JA, Xu J, Kapogiannis BG, Rudy B, Gonin R, Liu N, Wilson CM, Worrell C, Squires KE. Immunogenicity and safety of the human papillomavirus 6, 11, 16, 18 vaccine in HIV-infected young women. Clin Infect Dis, 2013; 57(5): 735–744.

133. Toft L, Tolstrup M, Muller M, Sehr P, Bonde J, Storgaard M, Ostergaard L, Sogaard OS. Comparison of the immunogenicity of Cervarix(R) and Gardasil(R) human papillomavirus vaccines for oncogenic non-vaccine serotypes HPV-31, HPV-33, and HPV-45 in HIV-infected adults. Hum Vaccin Immunother, 2014; 10(5): 1147–1154.

134. Giacomet V, Penagini F, Trabattoni D, Vigano A, Rainone V, Bernazzani G, Bonardi CM, Clerici M, Bedogni G, Zuccotti GV. Safety and immunogenicity of a quadrivalent human papillomavirus vaccine in HIV-infected and HIV-negative adolescents and young adults. Vaccine, 2014; 32(43): 5657–5661.

135. Kojic EM, Rana AI, Cu-Uvin S. Human papillomavirus in HIV-infected women: need for increased coverage. Expert Rev Vaccines, 2016; 15(1): 105-117

136. Masur H, Brooks JT, Benson CA, Holmes KK, Pau AK, Kaplan JE. Prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: updated guidelines from the Centers for Disease Control and Prevention, National Institutes of Health, and HIV medicine Association of the Infectious Diseases Society of America. Clin Infect Dis, 2014; 58(9): 1308–1311.

137. Bower M, Mazhar D, Stebbing J. Should cervical cancer be an acquired immunodeficiency syndrome-defining cancer? J Clin Oncol, 2006; 24(16): 2417-2419

138. Bruni L, Diaz M, Castellsagué X, Ferrer E, Bosch FX, de Sanjosé S. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. J Infect Dis. 2010 Dec 15; 202(12):1789-99.

139. Tate DR, Anderson RJ. Recrudescence of cervical dysplasia among women who are infected with human immunodeficiency virus: a case-control analysis. Am J Obstet Gynecol, 2002; 186: 880-882

140. Oehler-Janne C, Huguet F, Provencher S, et al. HIV-specific differences in outcome of squamous cell carcinoma of the anal canal: a multicentric cohort study of HIV-positive patients receiving highly active antiretroviral therapy. J Clin Oncol, 2008; 26(15): 2550-2557

141. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol. 2008 Dec 10;26(35):5802-12.

142. Ward D. Cancer in Zimbabwe: Can we ease the suffering? Better HealthCare for Africa, Word Press. 2011

143. Allahverdipour, H. & Emami, A. (2010). Perceptions of cervical cancer threat, benefits, and barriers of Papanicolaou smear screening for women in Iran. Women & Health, 47(3), 23-37.

144. Baranoski, A., Horsburgh, C., Cupples, L., Aschengrau, A. & Stier, E. (2011). Risk factors for nonadherence with Pap testing in HIV-infected women. Journal of Women's Health, 20(00), 1-9.

145. Finocchario-Kessler S, Wexler C, Maloba M, Mabachi N, Ndikum-Moffor F, Bukusi E. Cervical cancer prevention and treatment research in Africa: a systematic review from a public health perspective.BMC Womens Health, 2016; 16(29): 1-25

146. Kojic EM, Rana AI, Cu-Uvin S. Human Papillomavirus Vaccination in HIV-infected Women: Need for Increased Coverage. Expert review of vaccines. 2016;15(1):105-117 doi:10.1586/14760584.2016.1110025

147. Coleman JS, Cespedes MS, Cu-Uvin S, Kosgei RJ, Maloba M, Anderson J et al. An insight into cervical cancer screening and treatment capacity in Sub Saharan Africa. J Low Genit Tract Dis. 2016;20(1):31-7

148. Finocchario-Kessler S. Wexler C. Maloba M. Mabachi N. Ndikum-Moffor F. Bukusi E. Cervical cancer prevention and treatment research in Africa: a systematic review from a public health perspective. BMC Womens Health. 2016; 16: 29

149. WHO. Comprehensive Cervical Cancer Control: A guide to essential practice. 2014. 2nd edition. Australia. ISBN 978 92 4 1548953

150. Briss P, Rimer B, Reilley B, Coates RC, Lee NC, Mullen P et al. Promoting Informed Decisions About Cancer Screening in Communities and Healthcare Systems. Am J Prev Med, 2004;26(1):67-80

151. Miot J, Wagner M, Khoury H, Rindress D, Goetghebeur M. Field testing of a multicriteria decision analysis (MCDA) framework for coverage of a screening test for cervical cancer in South Africa. Cost Effectiveness and Resource Allocation, 2012; 10:2

152. Pedersen K, Sorbye SW, Burger EA, Lonnberg S, Kristiansen IS. Using decision-analytic modeling to isolate interventions that are feasible, efficient and optimal: an application from the Norwegian cervical cancer-screening program. Value in Health, 2015;18: 1088-1097

153. Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute For Clinical Excellence (NICE). Lancet, 2002; 360: 711–715

154. Goldie SJ, Goldhaber-Fiebert JD, Garnett GP. Chapter 18: Public health policy for cervical cancer prevention: The role of decision science, economic evaluation, and mathematical modelling. Vaccine, 2006; 24S3: S3/155–S3/163

APPENDICES

Appendix 1: PRISMA-P Checklist for the prevention protocol

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X☐	☐	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	X☐	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X☐	☐	
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X☐	☐	
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X☐	☐	
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	X☐	
Support					
Sources	5a	Indicate sources of financial or other support for the review	X☐	☐	
Sponsor	5b	Provide name for the review funder and/or sponsor	X☐	☐	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	X☐	☐	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X☐	☐	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X☐	☐	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X☐	☐	

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X☐	☐	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	X☐	☐	
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X☐	☐	
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X☐	☐	
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X☐	☐	
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X☐	☐	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X☐	☐	
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	X☐	☐	
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X☐	☐	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	X☐	☐	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X☐	☐	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X☐	☐	

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X☐	☐	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X☐	☐	

Appendix 2: Search strategy for the prevention systematic review

OvidSP Search Strategy (Medline and Embase) for prevention of CC

1. Cervi* canc*.mp. [mp=title, abstract, full text, caption text]
2. cervi* neoplas*.mp. [mp=title, abstract, full text, caption text]
3. cervi* carcinom*.mp. [mp=title, abstract, full text, caption text]
4. cervi* dysplas*.mp. [mp=title, abstract, full text, caption text]
5. cervi* intraepithelial neoplas*.mp. [mp=title, abstract, full text, caption text]
6. prevent* or screen*.mp. [mp=title, abstract, full text, caption text]
7. pap smear*.mp. [mp=title, abstract, full text, caption text]
8. colposcopy.mp. [mp=title, abstract, full text, caption text]
9. hpv adj3 vaccin*.mp. [mp=title, abstract, full text, caption text]
10. HIV positive.mp. [mp=title, abstract, full text, caption text]
11. hiv seropositiv*.mp. [mp=title, abstract, full text, caption text]
12. hiv.mp. [mp=title, abstract, full text, caption text]
13. developing countr*.mp. [mp=title, abstract, full text, caption text]
14. underdeveloped countr*.mp. [mp=title, abstract, full text, caption text]
15. low income countr*.mp. [mp=title, abstract, full text, caption text]
16. low resource countr*.mp. [mp=title, abstract, full text, caption text]
17. low resource setting*.mp. [mp=title, abstract, full text, caption text]
18. developing countries.mp. [mp=title, abstract, full text, caption text]
19. 1 or 2 or 3 or 4 or 5
20. 6 or 7 or 8 or 9
21. 10 or 11 or 12
22. 13 or 14 or 15 or 16 or 17 or 18
23. 19 and 20 and 21 and 22

PubMed Search Strategy for prevention of CC

1. Cervical Neoplasm, Uterine OR Cervical Neoplasms, Uterine OR Neoplasm, Uterine Cervical OR Neoplasms, Uterine Cervical OR Uterine Cervical Neoplasm OR Neoplasms, Cervical OR Cervical Neoplasms OR Cervical Neoplasm OR Neoplasm, Cervical OR Neoplasms, Cervix OR Cervix Neoplasms OR Cervix Neoplasm OR Neoplasm, Cervix OR Cancer of the Uterine Cervix OR Cancer of the Cervix OR Cervical Cancer OR Uterine Cervical Cancer OR Cancer, Uterine Cervical OR Cancers, Uterine Cervical OR Cervical Cancer, Uterine OR Cervical Cancers, Uterine OR Uterine Cervical Cancers OR Cancer of Cervix OR Cervix Cancer OR Cancer, Cervix OR Cancers, Cervix
2. Test, Papanicolaou OR Pap Test OR Test, Pap OR Pap Smear OR Smear, Pap OR Papanicolaou Smear OR Smear, Papanicolaou OR screening OR screenings OR visual inspection with acetic acid OR hpv vaccination OR vaccination, hpv OR hpv dna analysis OR cytology OR prevention of cervical cancer OR cervical cancer, prevention OR cervical cancer, screening
3. hiv seropositivity OR hiv seropositivities or seropositivities, hiv OR hiv positive OR hiv or seropositivity, hiv OR AIDS positivity OR AIDS
4. Developing Countries OR Africa OR Africa, Northern OR Africa South of the Sahara OR Africa, Central OR Africa, Eastern OR Africa, Southern OR Africa, Western OR

Asia OR Asia, Central OR Asia, Southeastern OR Asia, Western OR Caribbean Region OR West Indies OR South America OR Latin America OR Central America OR Afghanistan OR Albania OR Algeria OR American Samoa OR Angola OR "Antigua and Barbuda" OR Argentina OR Armenia OR Azerbaijan OR Bahrain OR Bangladesh OR Barbados OR Benin OR Belarus OR Belize OR Bhutan OR Bolivia OR Bosnia-Herzegovina OR Botswana OR Brazil OR Bulgaria OR Burkina Faso OR Burundi OR Cambodia OR Cameroon OR Cape Verde OR Central African Republic OR Chad OR Chile OR China OR Colombia OR Comoros OR Congo OR Costa Rica OR Cote d'Ivoire OR Croatia OR Cuba OR Cyprus OR Czechoslovakia OR Czech Republic OR Slovakia OR Djibouti OR "Democratic Republic of the Congo" OR Dominica OR Dominican Republic OR East Timor OR Ecuador OR Egypt OR El Salvador OR Eritrea OR Estonia OR Ethiopia OR Fiji OR Gabon OR Gambia OR "Georgia (Republic)" OR Ghana OR Greece OR Grenada OR Guatemala OR Guinea OR Guinea-Bissau OR Guam OR Guyana OR Haiti OR Honduras OR Hungary OR India OR Indonesia OR Iran OR Iraq OR Jamaica OR Jordan OR Kazakhstan OR Kenya OR Korea OR Kosovo OR Kyrgyzstan OR Laos OR Latvia OR Lebanon OR Lesotho OR Liberia OR Libya OR Lithuania OR Macedonia OR Madagascar OR Malaysia OR Malawi OR Mali OR Malta OR Mauritania OR Mauritius OR Mexico OR Micronesia OR Middle East OR Moldova OR Mongolia OR Montenegro OR Morocco OR Mozambique OR Myanmar OR Namibia OR Nepal OR Netherlands Antilles OR New Caledonia OR Nicaragua OR Niger OR Nigeria OR Oman OR Pakistan OR Palau OR Panama OR Papua New Guinea OR Paraguay OR Peru OR Philippines OR Poland OR Portugal OR Puerto Rico OR Romania OR Russia OR "Russia (Pre-1917)" OR Rwanda OR "Saint Kitts and Nevis" OR Saint Lucia OR "Saint Vincent and the Grenadines" OR Samoa OR Saudi Arabia OR Senegal OR Serbia OR Montenegro OR Seychelles OR Sierra Leone OR Slovenia OR Sri Lanka OR Somalia OR South Africa OR Sudan OR Suriname OR Swaziland OR Syria OR Tajikistan OR Tanzania OR Thailand OR Togo OR Tonga OR "Trinidad and Tobago" OR Tunisia OR Turkey OR Turkmenistan OR Uganda OR Ukraine OR Uruguay OR USSR OR Uzbekistan OR Vanuatu OR Venezuela OR Vietnam OR Yemen OR Yugoslavia OR Zambia OR Zimbabwe

Appendix 3: Full-text screening form to the prevention systematic review

Reference details												
A1. Ref ID												
A2. 1st Author (pub. year)												
A3. Title of article												
A4. Journal												
A5. Publication type	Paper										Abstract	
A6. Assessor's name	XX		XX		XX		XX		XX		XX	
A7. Date												

B. Study included in systematic review:

Yes[1]		No[2]	

Reason(s) for exclusion (if excluded):	Yes[1]	No[2]
C1. Prevention methods for cervical cancer in HIV seropositive women not investigated.		
C2. Unrepresentative sample		
C3. Done in developed countries		
C4. Review/editorial article		
C5. Duplicate (Insert Ref ID of other study)	Ref ID:	
C6. Other please specify:		

Appendix 4: Data extraction form for the prevention systematic review

A. Reference details									
A1. Ref ID, 1st author, title, publication year,									
A2. Assessor's name and date of assessment									
B. Study details									
B1. Name of study/cohort									
B2. Design	RCT		Prospective cohort		Other				
B2A. If other:									
B3. Country, setting									
C. Cervical cancer prevention methods									
C1. Pap smear/cytology	Yes		No						
C2. HPV DNA	Yes		No						
C3. VIA/C	Yes		No						
C4. HPV vaccination	Yes		No						
C5. Other measures (list):									
C6. How ascertained	Prospectively		Retrospectively						
C7. Age recorded									
C8. Age referred to									
D. Available participant numbers									
D1. Baseline	Yes		No		If yes, number				
D2. Excluded	Yes		No		If yes, number				
D3. Lost to follow-up	Yes		No		If yes, number				
D4. Included in analysis	Yes		No		If yes, number				
D5. All accounted for?	Yes		No						
E. Analysis									
E1. How results analysed	Descriptive/ Trend		Logistic regression		Linear regression		Other		
E1A. If other:									
E2. Included in analysis	Women								
E3. Only significant results presented?	Yes		No						
F. Summary of results									
F1. Prevalence/Mean difference	Yes		No						
F2. Odds/Risk ratios	Yes		No						
F3. Regression coefficients	Yes		No						
F4. Confidence intervals (CIs)/ P-value/standard errors (SE)	Yes		No						
F5. Other	Yes		No						
F5A. If other									
G. References for screening									
G1. Reference numbers									

H. Effect estimates

Association tested	Number analysed	Type of effect estimate and category comparison/value of unit change	Effect estimate	95% CI; SE; p-value	Confounders included in analysis
1.					
2.					

Appendix 5: Amended Newcastle-Ottawa Quality Assessment Scale for both prevention and treatment systematic reviews

Note: A study can be awarded a maximum of two stars for each numbered item – (except number 2 and 3 under case-control studies and number 5 under cohort studies).

CASE-CONTROL STUDIES

Selection

1) Is the case definition adequate?
a) Yes, with independent validation **
b) Yes, e.g record linkage or based on self-reports*
c) No description
2) Representativeness of the cases
a) Consecutive or obviously representative series of cases **
b) Potential for selection biases or not stated
3) Selection of Controls
a) Community controls **
b) Hospital controls *
c) No description
4) Definition of Controls
a) No history of disease (endpoint) *
b) No description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
a) Study controls for cervical cancer treatment modality (age, HIV status.) * *
b) Study controls for any additional factor * (parity, socio-economic status.)

Exposure

1) Ascertainment of exposure
a) Secure record (surgical/medical records, pathological/laboratory records) **
b) Structured interview where blind to case/control status *
c) Interview not blinded to case/control status
d) Written self-report or medical record only
e) No description
2) Same method of ascertainment for cases and controls
a) Yes *
b) No
3) Non-Response rate
a) Same rate for both groups *
b) Non respondents described
c) Rate different and no designation

COHORT STUDIES

Selection

1) Representativeness of the exposed cohort
a) Truly representative of the source population. **
b) Somewhat representative of the source population. *
c) Selected group of users e.g. nurses, volunteers.
d) No description of the derivation of the cohort.
2) Ascertainment of cervical cancer and HIV status
a) Prospectively from participants through diagnosis, laboratory tests and blood tests. **
b) Retrospectively collected with attempts to reduce recall bias (e.g. medical records and structured interview techniques). *
c) Retrospectively collected without attempts to reduce recall bias.

d) No description.

Comparability

3) Comparability of cohorts on the basis of the design/analysis

a) Study controls for HIV seropositive cervical cancer women. **

b) Study controls for any additional relevant factors (e.g. age, other diseases). *

c) Only unadjusted results presented.

Outcome

4) Assessment of prevention and treatment modality

a) Objective methods (prognosis, morbidity or mortality rates). **

b) Self-reported using validated questionnaire/diary/interview. *

c) Self-report.

d) No description.

5) Adequacy of cohort follow-up

a) Complete follow up - all subjects accounted for. *

b) Subjects lost to follow up unlikely to introduce bias (≥75% follow-up or description provided of those lost). *

c) <75% follow-up and no description of those lost.

d) No statement.

RANDOMISED CLINICAL TRIALS

Selection

1) Representativeness of the exposed group

a) Truly representative of the source population. **

b) Somewhat representative of the source population. *

c) Selected group of users e.g. patients, volunteers.

d) No description of the derivation of the group.

2) Ascertainment of cervical cancer and HIV status

a) Prospectively from participants through diagnosis, laboratory tests and blood tests. **

b) Retrospectively collected with attempts to reduce recall bias (e.g. medical records and structured interview techniques). *

c) Retrospectively collected without attempts to reduce recall bias.

d) No description.

Comparability

3) Comparability of groups on the basis of the design/analysis

a) Study controls for HIV seropositive cervical cancer women. **

b) Study controls for any additional relevant factors (e.g. age, other diseases). *

c) Only unadjusted results presented.

Outcome

4) Assessment of prevention modality

a) Objective methods (prognosis, morbidity or mortality rates). **

b) Self-reported using validated questionnaire/diary/interview. *

c) Self-report.

d) No description.

5) Adequacy of trial follow-up

a) Complete follow up - all subjects accounted for. *

b) Subjects lost to follow up unlikely to introduce bias (≥75% follow-up or description provided of those lost). *

c) <75% follow-up and no description of those lost.

d) No statement.

Appendix 6: PRISMA-P Checklist for the treatment protocol

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X☐	☐	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	X☐	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X☐	☐	
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X☐	☐	
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X☐	☐	
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	X☐	
Support					
Sources	5a	Indicate sources of financial or other support for the review	X☐	☐	
Sponsor	5b	Provide name for the review funder and/or sponsor	X☐	☐	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	X☐	☐	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X☐	☐	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X☐	☐	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X☐	☐	

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X☐	☐	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	X☐	☐	
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X☐	☐	
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X☐	☐	
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X☐	☐	
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X☐	☐	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X☐	☐	
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	X☐	☐	
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X☐	☐	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	X☐	☐	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X☐	☐	

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X☐	☐	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X☐	☐	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X☐	☐	

Appendix 7: Search strategy for the treatment systematic review

OvidSP search strategy for treatment of cervical cancer in HIV-seropositive women

	Search Terms
1.	Cervi* canc*.mp. [mp=title, abstract, full text, caption text]
2.	cervi* neoplas*.mp. [mp=title, abstract, full text, caption text]
3.	cervi* carcinom*.mp. [mp=title, abstract, full text, caption text]
4.	cervi* dysplas*.mp. [mp=title, abstract, full text, caption text]
5.	cervi* intraepithelial neoplas*.mp. [mp=title, abstract, full text, caption text]
6.	treat* or therap*.mp. [mp=title, abstract, full text, caption text]
7.	chemotherap* .mp. [mp=title, abstract, full text, caption text]
8.	surger*.mp. [mp=title, abstract, full text, caption text]
9.	radiation adj3 therap*.mp. [mp=title, abstract, full text, caption text]
10.	cryotherap*.mp. [mp=title, abstract, full text, caption text]
11.	HIV positive.mp. [mp=title, abstract, full text, caption text]
12.	hiv seropositiv*.mp. [mp=title, abstract, full text, caption text]
13.	hiv.mp. [mp=title, abstract, full text, caption text]
14.	developing countr*.mp. [mp=title, abstract, full text, caption text]
15.	underdeveloped countr*.mp. [mp=title, abstract, full text, caption text]
16.	low income countr*.mp. [mp=title, abstract, full text, caption text]
17.	low resource countr*.mp. [mp=title, abstract, full text, caption text]
18.	low resource setting*.mp. [mp=title, abstract, full text, caption text]
19.	developing countries.mp. [mp=title, abstract, full text, caption text]
20.	1 or 2 or 3 or 4 or 5
21.	6 or 7 or 8 or 9 or 10
22.	11 or 12 or 13
23.	14 or 15 or 16 or 17 or 18 or 19
24.	20 and 21 and 22 and 23

PubMed search strategy for treatment of cervical cancer in HIV-seropositive women

1. Cervical Neoplasm, Uterine OR Cervical Neoplasms, Uterine OR Neoplasm, Uterine Cervical OR Neoplasms, Uterine Cervical OR Uterine Cervical Neoplasm OR Neoplasms, Cervical OR Cervical Neoplasms OR Cervical Neoplasm OR Neoplasm, Cervical OR Neoplasms, Cervix OR Cervix Neoplasms OR Cervix Neoplasm OR Neoplasm, Cervix OR Cancer of the Uterine Cervix OR Cancer of the Cervix OR Cervical Cancer OR Uterine Cervical Cancer OR Cancer, Uterine Cervical OR Cancers, Uterine Cervical OR Cervical Cancer, Uterine OR Cervical Cancers, Uterine OR Uterine Cervical Cancers OR Cancer of Cervix OR Cervix Cancer OR Cancer, Cervix OR Cancers, Cervix
2. Treatment OR therapy OR chemotherapy OR surgery OR radiation OR radiotherapy OR radiation therapy OR cryotherapy OR loop electrosurgical excision procedure OR LEEP
3. hiv seropositivity OR hiv seropositivities or seropositivities, hiv OR hiv positive OR hiv or seropositivity, hiv OR AIDS positivity OR AIDS
4. Developing Countries OR Africa OR Africa, Northern OR Africa South of the Sahara OR Africa, Central OR Africa, Eastern OR Africa, Southern OR Africa, Western OR Asia OR Asia, Central OR Asia, Southeastern OR Asia, Western OR Caribbean Region OR West Indies OR South America OR Latin America OR Central America OR

Afghanistan OR Albania OR Algeria OR American Samoa OR Angola OR "Antigua and Barbuda" OR Argentina OR Armenia OR Azerbaijan OR Bahrain OR Bangladesh OR Barbados OR Benin OR Belarus OR Belize OR Bhutan OR Bolivia OR Bosnia-Herzegovina OR Botswana OR Brazil OR Bulgaria OR Burkina Faso OR Burundi OR Cambodia OR Cameroon OR Cape Verde OR Central African Republic OR Chad OR Chile OR China OR Colombia OR Comoros OR Congo OR Costa Rica OR Cote d'Ivoire OR Croatia OR Cuba OR Cyprus OR Czechoslovakia OR Czech Republic OR Slovakia OR Djibouti OR "Democratic Republic of the Congo" OR Dominica OR Dominican Republic OR East Timor OR Ecuador OR Egypt OR El Salvador OR Eritrea OR Estonia OR Ethiopia OR Fiji OR Gabon OR Gambia OR "Georgia (Republic)" OR Ghana OR Greece OR Grenada OR Guatemala OR Guinea OR Guinea-Bissau OR Guam OR Guyana OR Haiti OR Honduras OR Hungary OR India OR Indonesia OR Iran OR Iraq OR Jamaica OR Jordan OR Kazakhstan OR Kenya OR Korea OR Kosovo OR Kyrgyzstan OR Laos OR Latvia OR Lebanon OR Lesotho OR Liberia OR Libya OR Lithuania OR Macedonia OR Madagascar OR Malaysia OR Malawi OR Mali OR Malta OR Mauritania OR Mauritius OR Mexico OR Micronesia OR Middle East OR Moldova OR Mongolia OR Montenegro OR Morocco OR Mozambique OR Myanmar OR Namibia OR Nepal OR Netherlands Antilles OR New Caledonia OR Nicaragua OR Niger OR Nigeria OR Oman OR Pakistan OR Palau OR Panama OR Papua New Guinea OR Paraguay OR Peru OR Philippines OR Poland OR Portugal OR Puerto Rico OR Romania OR Russia OR "Russia (Pre-1917)" OR Rwanda OR "Saint Kitts and Nevis" OR Saint Lucia OR "Saint Vincent and the Grenadines" OR Samoa OR Saudi Arabia OR Senegal OR Serbia OR Montenegro OR Seychelles OR Sierra Leone OR Slovenia OR Sri Lanka OR Somalia OR South Africa OR Sudan OR Suriname OR Swaziland OR Syria OR Tajikistan OR Tanzania OR Thailand OR Togo OR Tonga OR "Trinidad and Tobago" OR Tunisia OR Turkey OR Turkmenistan OR Uganda OR Ukraine OR Uruguay OR USSR OR Uzbekistan OR Vanuatu OR Venezuela OR Vietnam OR Yemen OR Yugoslavia OR Zambia OR Zimbabwe

Appendix 8: Full-text screening form for the treatment systematic review

Reference details												
A1. Ref ID												
A2. 1st Author (pub. year)												
A3. Title of article												
A4. Journal												
A5. Publication type	Paper										Abstract	
A6. Assessor's name	XX		XX		XX		XX		XX		XX	
A7. Date												

B. Study included in systematic review:

Yes[1]		No[2]	

Reason(s) for exclusion (if excluded):	Yes[1]	No[2]
C1. Treatment modalities for cervical cancer in HIV seropositive women not investigated.		
C2. Unrepresentative sample		
C3. Done in developed countries		
C4. Review/editorial article		
C5. Duplicate (Insert Ref ID of other study)	Ref ID:	
C6. Other please specify:		

Appendix 9: Data extraction form for the treatment systematic review

A. Reference details								
A1. Ref ID, 1st author, title, publication year,								
A2. Assessor's name and date of assessment								
B. Study details								
B1. Name of study/cohort								
B2. Design	RCT		Prospective cohort		Other			
B2A. If other:								
B3. Country, setting								
C. Cervical cancer treatment modalities								
C2. Type of treatment	Surgery		Chemotherapy		Radiation Therapy		Other	
C2A. If other please describe								
C3. How ascertained	Self-reported		Objective methods					
C4. Age ascertained								
C5A. If other:								
D. Available participant numbers								
D1. Baseline	Yes		No		If yes, number			
D2. Excluded	Yes		No		If yes, number			
D3. Lost to follow-up	Yes		No		If yes, number			
D4. Included in analysis	Yes		No		If yes, number			
D5. All accounted for?	Yes		No					
E. Analysis								
E1. How results analysed	Descriptive/ Trend		Logistic regression		Linear regression		Other	
E1A. If other:								
E2. Included in analysis	Women							
E3. Only significant results presented?	Yes		No					
F. Summary of results								
F1. Prevalence/Mean difference	Yes		No					
F2. Odds/Risk ratios	Yes		No					
F3. Regression coefficients	Yes		No					
F4. Confidence intervals (CIs)/ P-value/standard errors (SE)	Yes		No					
F5. Other	Yes		No					
F5A. If other								
G. References for screening								
G1. Reference numbers								

H. Effect estimates

Association tested	Number analysed	Type of effect estimate and category comparison/value of unit change	Effect estimate	95% CI; SE; p-value	Confounders included in analysis
1.					
2.					

Appendix 10: KAP study information sheet

The epidemiology and knowledge about/concerning cervical cancer in Zimbabwe

Good day,

My name is Witness Mapanga, a PhD Epidemiology student at the School of Health Systems and Public Health, University of Pretoria, South Africa. I am conducting a cross-sectional survey to understand the knowledge, attitude and practices of young people (15-24 year olds) in Zimbabwe towards cervical cancer, screening, HPV and vaccination. The study is being conducted in high schools and universities in five provinces in Zimbabwe.

I am interested to learn more from you, so that we can gain insights on how young people understand about cervical cancer.

Can I please invite you to participate in the study?

Duration of completing the self-administered questionnaire

Completing the questionnaire will last approximately 30-45 minutes.

Voluntary participation

Participation is entirely voluntary. It is up to you to decide to take part in the interview. Those who are under 18 years require parental consent and their assent to take part. Also, be informed that you will not be inconvenienced if you decide not to take part in the interview.

Risks

There are no risks associated with participation.

Confidentiality

No one except the study researchers will have access to the study questionnaire, including signed consent forms. In sharing the findings, no specific name or any other identifying information will be included in the report. Instead codes such as A and B will be assigned to participant names.

Approval and anticipated benefits of the study

The study has been cleared by the Research Ethics Committee, Faculty of Health Sciences, University of Pretoria (Ethics Reference Number: 146/2016 and the Medical Research Council of Zimbabwe (Approval Number: MRCZ/A/2135. It is anticipated the study will help contribute to new ideas and insights, especially on how young people may be involved and incorporated in national strategies on prevention of cervical cancer.

Questions

Should you have any questions pertaining to this study feel free to contact me, Witness Mapanga on witnessmapanga@yahoo.co.uk or +263775142253.

If you have any questions concerning this study or consent form beyond those answered by the investigator, including questions about the research, your rights as a research participant or research-related injuries; or if you feel that you have been treated unfairly and would like to talk to someone other than a member of the research team, please feel free to contact the Medical Research Council of Zimbabwe (MRCZ) on telephone (04)791792 or (04) 791193 and cell phone lines 0772 433 166 or 0779 439 564. The MRCZ Offices are located at the National Institute of Health Research premises at Corner Josiah Tongogara and Mazowe Avenue in Harare.

Thank you for considering participating in the study.

Appendix 11: KAP study adult consent form

The epidemiology and knowledge about/concerning cervical cancer in Zimbabwe.

Principal Investigator: Witness Mapanga [University of Pretoria, *PhD student)*]
Phone number(s):+263775142253 or +263784294543

What you should know about this research study:

- We give you this consent so that you may read about the purpose, risks, and benefits of this research study.
- You have the right to refuse to take part, or agree to take part now and change your mind later.
- Whatever you decide, it will not affect your regular care.
- Please review this consent form carefully. Ask any questions before you make a decision.
- Your participation is voluntary.

PURPOSE

You are being asked to participate in a research study of ***young people's knowledge of the risks associated with cervical cancer, current screening methods and vaccination.*** The purpose of the study is **to obtain information that will be used to help the government develop better and more effective cervical cancer awareness programmes; education materials and proper policies.** You were randomly selected as a possible participant in this study because **the study is targeting young people aged between 15 and 24 years. You will be part of 600 young people whom we are targeting to participate in this study.**

PROCEDURES AND DURATION

If you decide to participate, you will be asked to fill-out a questionnaire which will take approximately 30 minutes to complete.

RISKS AND DISCOMFORTS

This research study will not pose any health, legal, economic or psychological risks to you and your personal details will not be made public.

BENEFITS AND/OR COMPENSATION

We anticipate this research study to produce information that might be relevant to cervical cancer policy makers and that will help with designing of primary communication strategies for cervical cancer among the young people.

CONFIDENTIALITY

If you indicate your willingness to participate in this study by signing this document, you will be asked to complete a questionnaire that have a series of questions pertaining to cervical cancer. Any information that is obtained in connection with this study that can be identified with you will remain confidential and will be disclosed only with your permission. Information will be archived at the School of Health Systems and Public Health, University of Pretoria, where the data will be retrieved and analysed. Data will only be accessed by study personnel and will not be publicized.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. If you decide not to participate in this study, your decision will not affect your future relations with this investigator and the University of Pretoria. If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without penalty.

SIGNATURE PAGE

OFFER TO ANSWER QUESTIONS

Before you sign this form, please ask any questions on any aspect of this study that is unclear to you. You may take as much time as necessary to think it over.

AUTHORIZATION

You are making a decision whether or not to participate in this study. Your signature indicates that you have read and understood the information provided above, have had all your questions answered, and have decided to participate.

_____ _____

Name of Research Participant (please print) Date

_____ _____

Signature of Participant Time

_____

_____ _____

Name of Staff Obtaining Consent Signature Date

_____

_____ _____

Name of Witness Signature Date

YOU WILL BE OFFERED A COPY OF THIS CONSENT FORM TO KEEP.

If you have any questions concerning this study or consent form beyond those answered by the investigator, including questions about the research, your rights as a research participant or research-related injuries; or if you feel that you have been treated unfairly and would like to talk to someone other than a member of the research team, please feel free to contact the Medical Research Council of Zimbabwe (MRCZ) on telephone (04)791792 or (04) 791193 and cell phone lines 0772 433 166 or 0779 439 564. The MRCZ Offices are located at the National Institute of Health Research premises at Corner Josiah Tongogara and Mazowe Avenue in Harare.

Appendix 12: KAP study parent consent form

The epidemiology and knowledge about/concerning cervical cancer in Zimbabwe.

Principal Investigator: Witness Mapanga [University of Pretoria, *PhD student)*]
Phone number(s):+263775142253 or +263784294543

What you should know about this research study:

- We give you this consent so that you may read about the purpose, risks, and benefits of this research study.
- You have the right to refuse to allow your child to take part, or agree for your child to take part now and change your mind later.
- Whatever you decide, it will not affect your child in any way.
- Your child has the right to refuse to take part in the study even if you give consent.
- Please review this consent form carefully. Ask any questions before you make a decision.
- Your choice to allow your child to participate is voluntary.

PURPOSE

You are being asked to allow your child to participate in a research study of ***young people's knowledge of the risks associated with cervical cancer, current screening methods and vaccination.*** The purpose of the study is **to obtain information that will be used to help the government develop better and more effective cervical cancer awareness programmes; education materials and proper policies.** Your child was selected as a possible participant in this study because **the study is targeting young people aged between 15 and 17 years. Your child will be part of 600 young people whom we are targeting to participate in this study.**

PROCEDURES AND DURATION

If you decide to allow your child to participate, your child will be asked to fill-out a questionnaire which will take approximately 30 minutes to complete.

RISKS AND DISCOMFORTS

This research study will not pose any health, legal, economic or psychological risks to your child and their personal details will not be made public.

BENEFITS AND/OR COMPENSATION

We anticipate this research study to produce information that might be relevant to cervical cancer policy makers and that will help with designing of primary communication strategies for cervical cancer among the young people.

CONFIDENTIALITY

If you indicate your willingness for your child to participate in this study by signing this document, your child will be asked to complete a questionnaire that have a series of questions pertaining to cervical cancer. Any information that is obtained in connection with

this study that can be identified with your child will remain confidential and will be disclosed only with your, and when appropriate, your child's permission. Information will be archived at the School of Health Systems and Public Health, University of Pretoria, where the data will be retrieved and analysed. Data will only be accessed by study personnel and will not be publicized.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. If you decide not to allow your child to participate in this study, your decision will not affect your or your child's future relations with this investigator and the University of Pretoria. If you decide to allow your child to participate, you and your child are free to withdraw your consent and assent and discontinue participation at any time without penalty.

OFFER TO ANSWER QUESTIONS

Before you sign this form, please ask any questions on any aspect of this study that is unclear to you. You may take as much time as necessary to think it over.

AUTHORIZATION

You are making a decision whether or not to allow your child to participate in this study. Your signature indicates that you have read and understood the information provided above, have had all your questions answered, and have decided to allow your child to participate.

The date you sign this document to enroll your child in this study, that is, today's date, must fall between the dates indicated on the approval stamp affixed to each page. These dates indicate that this form is valid when you enroll your child in the study but do not reflect how long your child may participate in the study. Each page of this informed consent form is stamped to indicate the form's validity as approved by the MRCZ.

_____ _____

Name of Parent (please print) Date

_____ _____

Signature of Parent or legally authorized representative Time

_____

Relationship to the Participant

_____

_____

Signature of Witness Signature of Research Staff

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.

If you have any questions concerning this study or consent form beyond those answered by the investigator, including questions about the research, your rights as a research participant or research-related injuries; or if you feel that you have been treated unfairly and would like to talk to someone other than a member of the research team, please feel free to contact the Medical Research Council of Zimbabwe (MRCZ) on telephone (04)791792 or (04) 791193 and cell phone lines 0772 433 166 or 0779 439 564. The MRCZ Offices are located at the National Institute of Health Research premises at Corner Josiah Tongogara and Mazowe Avenue in Harare.

Appendix 13: KAP study children's assent form

The epidemiology and knowledge about/concerning cervical cancer in Zimbabwe.

Principal Investigator: Witness Mapanga [University of Pretoria, PhD student)]
Phone number(s):+263775142253 or +263784294543
We are doing a research study to find out about ***young people's knowledge of the risks associated with cervical cancer, current screening methods and vaccination.*** The purpose of the study is ***to obtain information that will be used to help the government develop better and more effective cervical cancer awareness programmes; education materials and proper policies.*** If you decide that you want to be part of this study, you will be asked to pertaining to your knowledge and attitude towards cervical cancer and this will take 20 minutes of your time.

When we are finished with this study we will write a report summarizing our findings. This report will not include your name or that you were in the study.

You do not have to be in this study if you do not want to be. If you decide to stop after we begin, that is okay too. Your parents know about the study too.

If you decide you want to be in this study, please sign your name.

PARTICIPANT'S ASSENT

My participation in this research study is voluntary. I understand that I have the right to refuse to take part in the study even if my parents have given consent. I have read and understood the above information, asked any questions which I may have and have agreed to participate. I will be given a copy of this form to keep.

Name of Participant

Signature of Participant

Date

_____

_____

Name of Witness Signature of Witness

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.

If you have any questions concerning this study or consent form beyond those answered by the investigator, including questions about the research, your rights as a research participant or research-related injuries; or if you feel that you have been treated unfairly and would like to talk to someone other than a member of the research team, please feel free to contact the Medical Research Council of Zimbabwe (MRCZ) on telephone (04)791792 or

(04) 791193 and cell phone lines 0772 433 166 or 0779 439 564. The MRCZ Offices are located at the National Institute of Health Research premises at Corner Josiah Tongogara and Mazowe Avenue in Harare.

Appendix 14: KAP study questionnaire

STUDY OBJECTIVE: To explore cervical cancer, HPV, other risk factors for cervical cancer, cervical cancer screening and HPV vaccination -related knowledge, attitudes, beliefs and health-seeking practices among the young (15 to 24 year olds) people in Zimbabwe.

☐ **Baseline data collection** **Date: ……. /……/……** dd/mm/yyyy

☐ **Follow-up data collection**

Study number: [ ] [ ] [ ] **Participant number: [ ] [ ] [ ]**

Information to read to participant

We wish to learn about your knowledge, attitudes and practices (beliefs) regarding cervical cancer, its risk factors including HPV and cervical cancer screening and HPV vaccination. We hope to know your needs and how best cervical cancer information might be brought to you, as well as what barriers are there to seeking cervical cancer information and services. The information you provide will be used to improve cervical cancer management in Zimbabwe. Your responses will not be released to anyone and will remain anonymous. Your name or any other information that might be associated with you will not be written on the questionnaire or be kept in any other records. Your participation is voluntary and you may choose to stop the interview at any time. Thank you for your assistance.

DEMOGRAPHIC QUESTIONS

1. How old are you? .....

What is your date of birth? ……. / …….. / …….. dd/mm/yyyy

2. What is your gender (sex)? Circle the right answer(s)

- Female 1
- Male 2

3. What is your marital status? Circle the right answer(s)

- Single 1
- Married 2
- Divorced 3
- Widowed 4
- Other (specify) 5

  ……..

4. What is the highest level of education you have completed? Circle the right answer(s)

- Tertiary education (college certificate, diploma, degree) 1
- Current university student 2
- High school (A-levels) 3
- Secondary school (O Levels) 4
- Current high school student 5
- Primary level 6

- No formal education 7

5. Where do you live? Circle the right answer(s)

- Urban
  High density suburb …… 1
  Low density suburb …… 2
- Rural ……. 3

6. Do you currently have paid employment? Circle the right answer(s)

- Yes 1
- No 2

  If yes, what do you do?

  ……

  If no, what do you do?

  ……

7. What is your religion? Circle the right answer(s)

- Christianity (roman catholic, protestant, Pentecostal) 1
- Traditional 2
- Apostolic Sect 3
- Muslim 4
- None 5
- Other (specify) 6

  ……..

8. How far do you live from the nearest clinic or hospital? Circle the right answer(s)

- 0-5kms 1
- 5-10kms 2
- 10-20kms 3
- More than 20kms 4

LIFESTYLE INFORMATION

9. Have you ever consumed alcohol? Circle the right answer(s)

- Yes 1
- No 2

If yes, are you a

- Current drinker 1
- Ex-drinker 2

How often?

- Everyday 1
- One to three days a week 2
- Once per month 3

Which type of alcohol?

- Bottled beer 1
- Whisky 2
- Opaque commercial sorghum beer (chibuku) 3
- Illicit home brewed beer (kachasu) 4
- Zimbabwe traditional drink (maheu) 5
- Other (specify) 6

…….

How much alcohol do you drink per week? Would you consider yourself as someone who drinks?

- at special occasions only 1
- 1-3 times per week 2
- 4-6 times per week 3
- everyday 4
- not applicable 9

What is the amount of alcohol you can say you drink per occasion?

- 1 glass 1
- 2-3 glasses 2
- 4 or more glasses 3
- not applicable 9

10. Do you smoke? Circle the right answer(s)

- Yes 1
- No 2

If yes, are you a

- Current smoker 1
- Ex-smoker (if quit at least one year prior to study) 2

How often?

- Everyday 1
- One to three days a week 2
- Once per month 3

Which type of tobacco?

- Cigarettes 1
- Snuff 2
- Pipes 3
- Tobacco twist (chimonera) 4
- Other (specify) 5

.....

How many cigarettes do you smoke per day?

- 1-10 cigarettes per day 1
- 11 to 20 cigarettes per day 2

- more than 20 cigarettes per day 3
- not applicable 9

FAMILY INFORMATION

11. What is the highest educational qualification of your parents/guardians? Circle the right answer(s)

- University education 1
- Higher educational qualification below degree level 2
- High school education (A-levels) 3
- Secondary school education (O-levels) 4
- Primary level education 5
- No formal education 6
- Other (specify) 7

  ……..

12. Have you, your family or close friends had cervical cancer? Circle the right answer(s)

	Yes	**No**	**Do not know**
You	1	2	3
Partner	1	2	3
Mother	1	2	3
Sister	1	2	3
Relative	1	2	3
Friend	1	2	3

HEALTH SEEKING BEHAVIOUR

13. Where do you usually go if you are sick, or to treat a general health problem? Circle the right answer(s)

	Yes	No
• Government or local council clinic or hospital	1	2
• Private clinic or hospital	1	2
• Traditional healers or herbalists	1	2
• Prophets or religious spiritual leaders	1	2
• Other (specify)	1	2

  ……..

14. How often do you generally seek health care at a clinic or hospital? Circle the right answer(s)

- Twice a year or more 1
- Once per year 2
- Less than once a year but at least twice in the past 5 years 3

- Once in past 5 years 4
- Never in past 5 years 5
- Other (specify) 6

……

CERVICAL CANCER KNOWLEDGE AND AWARENESS

	Yes	No
15. Do you know a disease called cervical cancer?	1	2

16. Where did you first learn about cervical cancer? Circle the right answer(s)

	Yes	No
• Newspapers or magazines	1	2
• Health workers	1	2
• Billboards	1	2
• Radio	1	2
• Television	1	2
• Posters, brochures and other printed materials	1	2
• Internet, social media (face book, WhatsApp, twitter)	1	2
• Family, friends, neighbours and colleagues	1	2
• Religious leaders	1	2
• Other (specify)	1	2

……..

17. In your opinion, how serious a disease is cervical cancer? Circle the right answer(s)
    - Very serious 1
    - Somewhat serious 2
    - Not very serious 3
18. The following may or may not increase a woman's chance of developing cervical cancer. Circle the right answer(s)

	Yes	No
• Infection with HPV (human papillomavirus)	1	2
• Smoking any cigarettes at all	1	2
• Having a weakened immune system (e.g. because of HIV/AIDS, immunosuppressant drugs or having a transplant)	1	2
• Long term use of the contraceptive pill	1	2
• Infection with a sexually transmitted infection (gonorrhoea, chlamydia, syphilis,)	1	2
• Having a sexual partner who is not circumcised	1	2
• Starting to have sex at a young age (before age 17)	1	2
• Having many sexual partners	1	2

- Having many children (more than five) 1 2
- Having a sexual partner with many previous partners 1 2
- Not going for regular smear (Pap) tests 1 2

19. In your opinion, who can be infected with cervical cancer? Circle the right answer(s)

	Yes	No
• Any woman	1	2
• Only old women	1	2
• Only poor women	1	2
• Only people living with HIV/AIDS	1	2
• Only alcoholics	1	2
• Only smokers	1	2
• Only drug users	1	2
• Only sex workers	1	2
• Other (explain)	1	2

……

20. Can cervical cancer be cured? Circle the right answer(s)
    - Yes 1
    - No 2
21. How can someone with cervical cancer be cured? Circle the right answer(s)

	Yes	No
• Chemotherapy	1	2
• Radiation therapy	1	2
• Surgery	1	2
• Drugs given by healthcare	1	2
• Herbal remedies	1	2
• Praying	1	2
• Not treatable	1	2
• Do not know	1	2
• Other (explain)	1	2

……..

CERVICAL CANCER ATTITUDES AND CARE-SEEKING BEHAVIOUR

22. Do you think you can get cervical cancer or your wife or girlfriend? (Ask respondent to please explain his/her answer.)
    - Yes (because) 1
      ……
      …….
    - No (because) 2
      ……
      ……..
23. What would be your reaction if you were found out that you have cervical cancer or your wife or girlfriend have cervical cancer? Circle the right answer(s)

	Agree	Somewhat	Do not agree
• Fear	1	2	3
• Surprise	1	2	3
• Shame	1	2	3
• Embarrassment	1	2	3
• Sadness or hopelessness	1	2	3
• Other	1	2	3

……

24. Who would you talk to about your illness (or your wife's or girlfriend's illness) if you had? Circle the right answer(s)

	Agree	Somewhat	Do not agree
• Doctor/other medical worker	1	2	3
• Spouse	1	2	3
• Parent	1	2	3
• Close friend	1	2	3
• Other family member	1	2	3
• No one	1	2	3
• Other	1	2	3

……

25. How expensive do you think cervical cancer diagnosis and treatment is in this country? Circle the right answer(s)

	Agree	Somewhat	Do not agree
• It is free of charge	1	2	3
• It is reasonably priced	1	2	3
• It is somewhat/moderately priced		2	3
• It is very expensive	1	2	3

CERVICAL CANCER ATTITUDES AND STIGMA

26. Do you know people who have/had cervical cancer? Circle the right answer(s)
    - Yes 1
    - No 2
27. In your community, how is a person who has cervical cancer usually regarded/treated? Circle the right answer(s)

	Yes	No
• Most people reject her	1	2
• Most people are friendly, but they generally try to avoid her	1	2
• The community mostly supports and helps her	1	2
• Other (explain)	1	2

……

…….

28. Which statement is closest to your feeling about women with cervical cancer? (Read the following choices) Circle the right answer(s)

	Agree	Somewhat	Do not agree
• "It is their problem and I can't get cervical cancer"	1	2	3
• "I feel they are of loose morals"	1	2	3
• "I feel they are poor people"	1	2	3
• "I feel they are ignorant people"	1	2	3
• "I feel compassion and desire to help"	1	2	3
• "I have no particular feeling"	1	2	3
• Other (explain) …… ……	1	2	3

29. Do you think that young people should be concerned about cervical cancer? Circle the right answer(s)

- Yes (go to 22a) 1
- No (go to 22b) 2

29a. Why? Circle the right answer(s)

- Cervical cancer affects everyone. 1
- Do not know 2
- Other (specify) 3
  ……

29b. Why not? Circle the right answer(s)

- Cervical cancer is for older women to worry about. 1
- Do not know 2
- Other (specify) 3
  ……..

CERVICAL CANCER AWARENESS AND INFORMATION

30. Do you feel well informed about cervical cancer? Circle the right answer(s)

- Yes 1
- No 2

31. Do you wish you could get more information about cervical cancer? Circle the right answer(s)

- Yes 1
- No 2

32. What are the sources of information that you think can most effectively reach young people like you with information on cervical cancer? Circle the right answer(s)

	Yes	No
• Internet, social media (face book, WhatsApp, twitter)	1	2
• Newspapers and magazines	1	2
• Radio	1	2

- TV 1 2
- Billboards 1 2
- Brochures, posters and other printed materials 1 2
- Health workers 1 2
- Family, friends, neighbours and colleagues 1 2
- Religious leaders 1 2
- Teachers 1 2
- Other (specify) 1 2

  ……..

33. What worries you the most when you think about cervical cancer?

  ……

  ……

  ……

  ……

HUMAN PAPILLOMAVIRUS (HPV) KNOWLEDGE

34. How can a person get HPV? Circle the right answer(s)

	Yes	No
• Kissing	1	2
• Holding or shaking hands	1	2
• Skin to skin contact	1	2
• Public toilet	1	2
• Unprotected sex	1	2
• Sex with a condom	1	2
• Sharing a spoon or cup	1	2
• Sneezing/coughing	1	2
• Do not know	1	2
• Other (explain)	1	2

  …….

	Yes	**No**	**Do not know**
35. HPV infection usually disappears on its own?	1	2	3
36. Is HPV infection a risk for cervical cancer?	1	2	3
37. HPV infection always leads to cervical cancer?	1	2	3

38. How can a person prevent getting infected with HPV? Circle the right answer(s)

	Yes	No
• Avoid kissing	1	2
• Avoid holding or shaking hands	1	2
• Avoid skin contact	1	2
• Avoid using public toilets	1	2
• Protected sex using a condom	1	2
• Avoid sharing a spoon or cup	1	2

- Covering mouth and nose when coughing or sneezing 1 2
- Do not know 1 2
- Other (explain) 1 2

……

SCREENING AND VACCINATION QUESTIONS

	Yes	No	Do not know
39. Have you ever heard of cervical cancer screening?	1	2	3
40. Have you ever heard of cervical cancer vaccination?	1	2	3

41. As far as you are aware, is there cervical cancer screening programme in Zimbabwe?
    - Yes 1
    - No 2
42. At what age are women first invited for cervical cancer screening in Zimbabwe?
    ……
    ……
43. Name any place where Pap smear, VIAC or cervical cancer screening is done?
    .....
    .....
44. Name your sources of information regarding the Pap smear, VIAC or cervical cancer screening in Zimbabwe?
    .....
    .....
45. As far as you are aware, is there vaccination to protect against cervical cancer in Zimbabwe?
    - Yes 1
    - No 2

    If yes, at what age is this offered? _____
46. Has your mother, sister or relative been screened or vaccinated against cervical cancer and HPV?
    - Yes 1
    - No 2

    If yes, who? .....

	Yes	No	Do not know
47. Have you been screened for cervical cancer?	1	2	3
48. Have you been vaccinated against HPV?	1	2	3
49. HPV vaccination protects against all types of HPV?	1	2	3
50. HPV vaccination protects against all Sexually Transmitted Infections (STIs)?	1	2	3

Appendix 15: Table of evidence – prevention systematic review

First author, year, study type	Purpose	Population & age	Country	Prevention method/tool	Study type	Outcome(s)	Results	Authors' Conclusions	Quality score
Bansil et al, 2015	To evaluate and compare performance of 3 cervical cancer screening options among HIV-infected women in Uganda	2,337 HIV-positive and HIV-negative women; 25 and 60 years	Uganda	-Visual inspection with acetic acid (VIA) -Vaginal careHPV -Cervical careHPV	Observational study without a control group	Clinical performance of cervical careHPV, vaginal careHPV and VIA	Among HIV-positive women, cervical careHPV had sensitivity and specificity of 94.3% and 62.4% respectively; vaginal careHPV had 80.0% sensitivity and 59.9% specificity; VIA had 77.1% sensitivity and 47.3% specificity. Among HIV-negative women, VIA had 93.8% sensitivity and 60.5% specificity; cervical careHPV had 81.3% sensitivity and 80.9% specificity; vaginal careHPV had 75.0% sensitivity and 81.9% specificity,	CareHPV™ performs better for screening cervical cancer among HIV-positive women when compared to VIA. VIA can be used as a triage method and reduce number of treatment by half	Moderate
Cholli et al, 2018	Assess feasibility and clinical outcomes of screening HIV-positive and HIV-negative Cameroonian women by pairing VIA/VILI-DC with careHPV (high-risk HPV nucleic acid test)	913 previously unscreened HIV-positive and HIV-negative women; >/=30years	Cameroon	(VIA/VILI-DC) CareHPV	Observational study without a control group	VIA/VILI-DC and careHPV co-testing strength among HIV-positive and HIV-negative women	For HIV-positive women: 8% (29/384) tested VIA/VILI-DC positive whilst 41% (157/384) tested positive on careHPV test (p<0.0001). HIV-positive women had more than twice VIA/VILI-DC positive results (n=29/384, 7.6%) than HIV-negative women (n=15/530, 2.8%) (p<0.0001) HIV-positive women were almost twice (1.9 times) more likely to test careHPV positive than HIV-negative for each VIA/VILI-DC result category	Exclusively relying only on VIA/VILI-DC will likely result in about 50% overtreatment rate. Due to their weaknesses, pairing VIA/VILI-DC and HPV DNA testing is effective.	Moderate
Chung et al, 2013	To compare Papanicolau smear, visual inspection with acetic acid and	500 HIV-positive women; 18 and 55 years	Kenya	Pap smear VIA HPV test Colposcopy-directed biopsy	Observational study without a control group	Sensitivity, specificity of Pap smear, VIA and HPV testing	Individually, the most sensitive test was Pap (ASCUS+) (92.7%), which was significantly more sensitive than VIA (62.7%; P < 0.001), Pap (HSIL+) (71.8%; P < 0.001) and HPV (83.6%; P = 0.04) (Table 3). HPV was significantly more sensitive than VIA (P <	Pap smear is a robust test among HIV-positive women regardless of immune status or ART duration. Pap	Moderate

	human papillomavirus cervical cancer screening methods among HIV-positive women by immune status and antiretroviral therapy						0.001) and Pap (HSIL+) (P = 0.04). Pap (HSIL+) (97.1%) was significantly more specific than VIA (65.9%; P < 0.001) and HPV (55.7%; P < 0.001), and VIA was more specific than HPV (P=0.006). The cervical screening method with the highest AUC was Pap (HSIL+) (0.85), which was significantly greater than VIA (0.64; P < 0.001), HPV (0.70; P < 0.001), Pap (ASCUS+) (0.71; P < 0.001) and Pap (LSIL+) (0.76; P < 0.001) Combining cervical screening methods did not significantly improve test sensitivity over using Pap (ASCUS+) alone. However, combining VIA and Pap (HSIL+) to confirm positive test results had greater specificity than Pap (HSIL+) alone (99.1 vs. 97.1%; P < 0.001).	(ASCUS+) had the highest sensitivity, combination of both Pap (HSIL+) and VIA positive had the highest specificity and Pap (HSIL+) had the highest AUC.	
Dartell et al, 2014	To examine the ability of VIA and HPV-testing to detect cytologically diagnosed high grade lesions or cancer (HSIL+)	3,603 HIV-positive and HIV-negative women; 24.4% were 29 years or younger, 35/1% were 30-39 years, 25.2% were 40-49 years and 15.3% were 50 years or older	Tanzania	Convectional cytology VIA HPV-DNA detection	Observational study without a control group	Sensitivity, specificity, positive predictive value and negative predictive value of VIA, HR HPV-testing compared to cytology	Among all women, VIA had a sensitivity of 28.5% (95% CI: 20.9–36.0) and a specificity of 96.5% (95% CI: 95.9–97.1). The sensitivity for VIA was higher in women from urban areas (39.0%) and among HIV positive women (50.0%). HPV-testing had a high sensitivity (94.2%; 95% CI: 90.2–98.1) and a somewhat lower specificity (82.8%; 95% CI: 81.6–84.1). The specificity was lowest among HIV positive women (58.2%) and among women 29 years or younger (74.7%). The VIA and HPV testing had a PPV ranging from 16.7 to 32.6% and from 7.2 to 22.9%, respectively. For both VIA and HPV-testing, the lowest PPV was seen among women below 29 years old. NPV was high for both VIA and HPV-testing (>99.6%) and reached up to 100% for HPV testing among women who were below 29 years and among women who were HIV positive.	HPV testing would be a better primary screening tool for cervical cancer in Sub-Saharan Africa, possibly with VIA as a secondary tool to increase specificity.	Moderate

Firnhaber et al, 2016	To compare VIA, Cytology and HPV-DNA testing among HIV-positive women	688 HIV-positive women; age IQR(33,44)	South Africa	Pap smear VIA HPV testing	Observational study without a control group		Progression to CIN-2+ was higher in women with positive VIA results (12.6%; 24/191) than those VIA-negative (4.4%; 19/432). HPV-positive women at baseline were more likely to progress to CIN-2+ (12.3%; 36/293) than those HPV-negative (2.1%; 7/329). Cytology-positive women at baseline were more likely to progress to CIN-2+ (9.6%; 37/384) than cytology-negative women (2.5%; 6/237). Approximately 10% (10.4%; 39/376) of women with CIN 1 at baseline progressed to CIN 2+. Women who were VIA or HPV positive at baseline were more likely to progress aIRR 1.85, CI 95% (1.46 to 2.36), aIRR 1.41 CI 95% (1.14 to 1.75) respectively.	Progression to CIN-2+ in HIV-infected women is significant when measured by baseline positive VIA, HPV or Pap and yearly screening by any method should be considered in this population if possible.	Moderate
Huchko et al, 2014	To determine the optimal strategy for cervical cancer screening in women with HIV infection by comparing two strategies: VIA and VIA followed by VILI in women with a positive VIA result	3462 HIV-positive women; 23-60 years	Kenya	VIA and VIA/VILI	Observational study with a control group	Positivity rate and PPV for VIA and VIA/VILI for CIN2+ among HIV-infected women	Screening positivity rate was 26.4% for VIA and 21.7% VIA/VILI (P=0.003) with a follow-up colposcopy rate of 96.6% and 96.3% respectively. The PPV of VIA for biopsy-confirmed CIN 2+ in a single round of screening was 35.2% VIA, compared with 38.2% for VIA/VILI (P = 0.41).	The absence of much differences between VIA and VIA/VILI in detection rates or PPV for CIN 2+ suggests that VIA, can be used alone as a cervical cancer screening strategy in low-income settings.	High
Huchko et al, 2015	To compare the diagnostic accuracy of VIA to VILI for cervical cancer	654 HIV-positive women; 23-65 years	Kenya	VIA and VILI	Randomised clinical trial	Test performance of VIA or VILI	The test positivity rates were 26.2% for VIA and 30.6% for VILI (p = 0.22). The rate of detection of CIN2+ was 7.7% in the VIA arm and 11.5% in the VILI arm (p = 0.10). Sensitivity and specificity were 84.0% and 78.6%, respectively, for VIA and 84.2% and	VIA and VILI had similar diagnostic accuracy and rates of CIN2+ detection among HIV-infected women.	High

	screening in HIV-infected women						76.4% for VILI. The positive and negative predictive values were 24.7% and 98.3% for VIA, and 31.7% and 97.4% for VILI. Among women with CD4+ count < 350, VILI had a significantly decreased specificity (66.2%) compared to VIA in the same group (83.9%, p = 0.02) and compared to VILI performed among women with CD4+ count >/= 350 (79.7%, p = 0.02).		
Joshi et al, 2013	To evaluate an accurate, affordable, and feasible method to screen and treat HIV-infected women so that cervical cancer can be prevented among them	1128 HIV-positive women; 21-60 years	India	VIA, VILI, Cytology, HPV testing, Colposcopy	Observational study without a control group	Concurrent performance of Cytology, HPV testing, VIA and VILI in detecting CIN2 and 3	The sensitivity, specificity, and positive predictive values for VIA to detect CIN2 and 3 lesions were 83.6, 88.8, and 27.7%, respectively; the corresponding values for VILI were 89.1, 89.3, and 30.1%; for cytology at ASCUS threshold were 63.3, 94.5, and 35.2%, and for HPV testing were 94.6, 77.4, and 17.8%, respectively. Although VIA had a higher sensitivity than cytology, it did not reach statistical significance. HPV testing was 100% sensitive in detecting CIN3 lesions; however it had significantly lower specificity than VIA, VILI, and cytology (P<0.001).	HPV testing, VILI, and VIA have a higher sensitivity in detecting high-grade CIN than that of conventional cytology. Sequential testing with VIA and VILI is the most feasible screening approach for cervical cancer screening in HIV-infected women in low-resource countries. When HPV testing becomes feasible and affordable, HPV testing followed by VIA/VILI may be considered.	Moderate
Kuhn et al, 2010	To evaluate the efficacy among HIV-infected women of a simpler, screen-and-treat strategy in which all women with a	6555 women, whom 956 were HIV-positive; 35-65 years	South Africa	HPV DNA based screen-and-treat and VIA-based screen-and-treat	Randomised clinical trial	Safety and efficacy of screen-and-treat among HIV-positive women	HPV DNA testing was highly effective in reducing the risk of CIN2+ by 36 months among both HIV-positive [relative risk (RR)=0.20, 95% confidence interval (CI) 0.06–0.69] and HIV-negative women (RR=0.31, 95% CI 0.20–0.50). The benefit of VIA-and-treat was less marked and only reached statistical significance in HIV-positive women	HPV-based screen-and-treat is safe and effective in HIV-positive women. A single round of screening with an HPV test followed by cryotherapy of all screen-positive women reduced high-	High

	positive screening test are treated with cryotherapy						(RR=0.51, 95% CI 0.29–0.89) and not in HIV-negative women (RR=0.76, 95% CI 0.52–1.1). The sensitivity of HPV DNA testing at enrolment to detect CIN2+ through 36 month was 94.4% in HIV-positive women, whereas the sensitivity of the VIA test was 63.9% in HIV-positive women. In the HPV and-treat group, there was a slightly lower rate of CIN2+ after cryotherapy among HIV-positive (2.8%) vs. HIV-negative (7.1%) women but this difference was of borderline significance (P=0.05). In the VIA-and-treat group, CIN2+ failure rates after cryotherapy were similar in HIV-positive (4.8%) and HIV-negative (2.8%) women	grade cervical cancer precursors (CIN2+) by 80% and this was sustained through 36 months. VIA-based screen-and-treat was significantly less effective, although better than no intervention in HIV-positive women	
Lim et al, 2011	To compare Pap smear readings to VIA findings among HIV-infected women in Phnom Penh, Cambodia	293 HIV-infected women;	Cambodia	Pap smear and VIA	Observational study without a control group	Degree of correlation between Pap smear and VIA findings	55 (19%) women screened positive on VIA; 25 (8.5%) women screened positive by Pap. Visual inspection with acetic acid detected 18 of the 25 patients with abnormal cytology and was normal in 7 women with abnormal cytology. 37 (67%) women with positive VIA were negative by cytology.	Our study shows a reasonable correlation between VIA and Pap smear, with VIA detecting more abnormalities than cytology. In the absence of Pap smear availability, VIA may be a reasonable cervical cancer screening method for HIV-infected women in Cambodia.	Low
Mabeya et al, 2012	To determine the accuracy of VIA versus Pap smear among HIV-infected women	150 HIV-infected women; 20-45 years	Kenya	Pap smear and VIA	Observational study without a control group	Accuracy of VIA versus conventional Pap smear as a screening tool for CIN/cancer among HIV-infected women with biopsy as the	Using AUC as an overall measure of screening accuracies and using CIN 1 or higher as the gold standard threshold, the performance of Pap smear is slightly better than VIA, but the difference is not significant (Pap smear: AUC = 0.596, VIA: AUC = 0.571, p-value = 0.64). When using CIN 2 or higher as the gold standard threshold, the performance of Pap smear and VIA are more comparable (Pap smear: AUC = 0.606, VIA: AUC = 0.603, p-value = 0.93). Using CIN2 or	Visual inspection with acetic acid is comparable to Pap smear and acceptable for screening HIV-infected women in resource-limited settings such as Western Kenya.	Moderate

						reference criterion standard	higher disease on biopsy as an end point, VIA has a sensitivity of 69.6% (95% CI = 55.1%-81.0%), specificity of 51.0% (95% CI = 41.5%-60.4%), PPV of 38.6% (95% CI = 28.8%-49.3%), and NPV of 79.1% (95% CI = 67.8%-87.2%). For conventional Pap smear, sensitivity was 52.5% (95% CI = 42.1%-71.5%), specificity was 66.3% (95% CI = 52.0%-71.2%), PPV was 39.7% (95% CI = 27.6%-51.8%), and NPV was 76.8% (95% CI = 67.0%-85.6%).		
Michelow et al, 2016	To evaluate the performance of the Cellslide(®) automated liquid-based cytology (LBC) system as a possible alternative to conventional cytology among HIV-positive women	348 HIV-positive women;18-65 years	South Africa	Cellslide(®) automated LBC	Observational study without a control group	Number of positive and negative samples tested using Cellslide(®)	For HSIL, Cellslide® showed sensitivity of 76.0% (95% CI: 64.8–85.1) and specificity of 91.0% (95% CI: 87.0–94.2), with a false-omission rate < 7%, compared with conventional cytology. When compared with conventional cytology, Cellslide® showed sensitivity of 89.6% (95% CI: 82.9–94.4) and specificity of 92.2% (95% CI: 87.8–95.4) for NILM, sensitivity of 70.2% (95% CI: 61.3–78.0) and specificity of 87.7% (95% CI: 82.6–91.7) for LSIL, and sensitivity of 100% (95% CI: 2.5–100) and specificity of 98.8% (95% CI: 97.1–99.7) for ASCH.	The performance of the Cellslide((R)) LBC system was similar to that of conventional cytology in this population of high-risk HIV-positive women, indicating that it may be introduced successfully as part of a cervical cancer screening programme.	Low
Mutyaba et al, 2010	To evaluate the 'see-see and treat' strategy and role of HIV on cervical cancer prevention in Uganda	5 105 HIV-negative and HIV-positive women; 20-60 years	Uganda	VIA/VILI and cryotherapy	Observational study without a control group	Detection rates by age-group and cervical lesion treatment	Detection rates per 1 000 women screened were higher among the older women (41-60 years) compared to women aged 20-40 years. They were accordingly 55% and 20% for inflammation, 10% and 2% for LGSIL, 5% and 2% for HGSIL, 6% and 1% for invasive cervical cancer. Of the 608 women, 103 (16%) were HIV positive. HIV positivity was associated with higher likelihood of inflammation (RR = 1.7; 95% CI: 1.2-2.4).	VIA/VILI used as a sole method for cervical cancer screening would entail significant false positive results. HIV seropositivity was associated with a higher prevalence of inflammatory cervical lesions. Cryotherapy	Low

							The 32 women with SIL (19 LGSIL and 13 HGSIL) underwent treatment by cryotherapy (31 women) or LEEP (1 woman). 1 woman had persistent LSIL and 1 had inflammation; both were HIV positive. Other 27 women had normal findings	treatment outcome was not conclusive due to limited follow-up time	
Ngou et al, 2015	To compare the Hybrid Capture 2 HPV DNA assay (HC2) and the INNO-LiPA HPV Genotyping Extra assay (INNO-LiPA) for cervical cancer screening in HIV-1-infected African women.	1224 HIV-positive women in Burkina Faso (N = 604) and South Africa (N = 620); 25-50 years	Burkina Faso and South Africa	HC2 and INNO-LiPA	Observational study without a control group	Agreement between HC2 and INNO-LiPA for detection of HR-HPV infection and compare their performances in diagnosing cervical lesions detected by cytology and histology	When considering the 13 hr-HPV types detected by HC2, 634 (51.8%) and 849 (69.4%) samples were positive by HC2 and INNO-LiPA, respectively. Agreement between assays was 73.9% [adjusted kappa coefficient value, 0.44 (95% confidence interval: 0.43 to 0.53)]. Agreement improved with analysis restricted to women with high-grade cervical lesions [adjusted kappa coefficient value, 0.83 (95% confidence interval: 0.74 to 0.91)]. The prevalence of hr-HPV, as determined by HC2 and INNO-LiPA, was 34.5% and 54.5%, respectively, in samples with normal cytology, 48.0% and 68.0%, respectively, in samples with atypical squamous cells of undetermined significance, 51.8% and 75.2%, respectively, in samples with low-grade SIL, and 86.3% and 89.8%, respectively, in samples with high-grade SIL/atypical squamous cells that cannot exclude HSIL. Sensitivity, specificity, positive, and negative predictive values for the diagnosis of histological high-grade lesions (CIN2+) were 88.8%, 55.2%, 24.7% and 96.7%, and 92.5%, 35.1%, 19.1% and 96.6% for HC2 and INNO-LiPA, respectively	HC2 has lower analytical sensitivity but higher specificity than INNO-LiPA for diagnosing high-grade lesions; the 2 tests presented a comparable clinical sensitivity. HC2 might be suitable for cervical cancer screening in HIV-1-infected African women, but its use in resource-limited settings merits to be further evaluated in comparison with other prevention strategies.	Moderate
Ngou et al, 2013	To compare careHPV and hybrid capture 2 assays for detection of high-risk human	149 HIV-1-infected African women (75 in Johannesburg, South Africa and	Burkina Faso and South Africa	careHPV and HC2	Observational study without a control group	Agreement in detecting HR-HPV between careHPV and HC2	The HR-HPV DNA detection rates were 37.6% and 34.9% for careHPV and HC2, respectively. Agreement between the two tests was 94.6% (95% confidence interval [CI], 89.7% to 97.7%) with a kappa value of 0.88 (95% CI, 0.81 to 0.96), indicating an excellent agreement.	CareHPV may be considered as suitable as HC2 for cervical cancer screening among HIV-infected African women.	Moderate

	Papillomavirus DNA in cervical samples from HIV-1-infected African women	74 in Ouagadougou, Burkina Faso); 25-50 years							
Obiri-Yeboah et al, 2017	To compare the performance of careHPV with HPV genotyping for the detection of cytological cervical squamous intraepithelial lesions (SIL)	175 women (94 HIV-1-seropositive and 81 HIV-seronegative women); >=18 years	Ghana	HPV Genotyping vs careHPV	Observational study with a control group	Agreement in detecting HR-HPV between careHPV and HPV genotyping	The inter-assay concordance was 94.3% (95%CI: 89.7-97.2%, kappa = 0.88), similar by HIV serostatus. The careHPV assay was equally sensitive among HIV-1 seropositive and seronegative women (97.3% vs. 95.7%, p = 0.50) and slightly more specific among HIV-seronegative women (85.0% vs. 93.1%, p = 0.10). CareHPV had good sensitivity (87.5%) but low specificity (52.1%) for the detection of low SIL or greater lesions, but its performance was superior to genotyping (87.5 and 38.8%, respectively). Reproducibility of careHPV, tested on 97 samples by the same individual was 82.5% (95%CI: 73.4-89.4%).	The performance characteristics of careHPV compared to genotyping suggest that this simpler and cheaper HPV detection assay could offer a suitable alternative for HPV screening in Ghana.	High
Obiri-Yeboah et al, 2017	To determine the acceptability, feasibility and performance of alternative self-collected vaginal samples for HPV detection using careHPV among Ghanaian women	194 women (97 HIV-positive); >=18 years	Ghana	Self-collected vaginal samples with care HPV	Observational study with a control group	Performance of self-collected cervico-vaginal samples compared to clinician collected samples	Overall HPV detection concordance was 94.2% (95%CI: 89.9-97.1), Kappa value of 0.88 (p < 0.0001), showing excellent agreement. This agreement was similar between HIV positive (93.8%) and negative (94.7%) women. Sensitivity and specificity of SC compared to CC were 92.6% (95%CI: 85.3-97.0) and 95.9% (95%CI: 89.8-98.8) respectively. The highest sensitivity was among HIV positive women (95.7%, 95%CI: 88.0-99.1) and highest specificity among HIV negative women (98.6%, 95%CI: 92.4-100). Overall, 76.3% women found SC very easy/easy to obtain, 57.7% preferred SC to CC and 61.9% felt SC would increase their	The feasibility, acceptability and performance of SC using careHPV support the use of this alternative form of HPV screening among Ghanaian women. This could be a potential new affordable strategy to improve uptake of the national cervical cancer screening programme.	Moderate

							likelihood to access cervical cancer screening.		
Sahasrabuddhe et al, 2012	To rigorously evaluate the clinical accuracy of VIA and cytology among HIV-infected women in Pune, India	303 nonpregnant HIV-infected women; 25-40 years	India	VIA Pap smear	Observational study without a control group	Sensitivity, specificity, PPV and NPV for VIA and Cytology	At CIN2+ disease threshold, the sensitivity, specificity and positive and negative predictive value estimates of VIA were 80, 82.6, 47.6 and 95.4% respectively, compared to 60.5, 59.6, 22.4 and 88.7% for the atypical squamous cells of undetermined significance or severe (ASCUS+) cut off on cytology, 60.5, 64.6, 24.8 and 89.4% for the low-grade squamous intraepithelial cells or severe (LSIL+) cut off on cytology and 20.9, 96.0, 50.0 and 86.3% for high-grade squamous intraepithelial lesion or severe (HSIL+) cut off on cytology. A similar pattern of results was found for women with the presence of carcinogenic HPV-positive CIN2+ disease, as well as for women with CD4+ cell counts <200 and <350 muL(-1) .	Overall, VIA performed better than cytology in this study with biologically rigorous endpoints and without verification bias, suggesting that VIA is a practical and useful alternative or adjunctive screening test for HIV-infected women.	Moderate
Wu et al, 2016	To measure the sensitivity, specificity and predictive values of p16INK4a ELISA for CIN2+.	1054 HIV-infected women; >=23 years	Kenya	p16(INK4a) ELISA	Observational study without a control group	Sensitivity, specificity and predictive values of p16INK4a ELISA	The p16INK4a cut-off value with the highest combined sensitivity (89.0%) and specificity (22.9%) for biopsy proven CIN2+ was 9 U/mL. The positive predictive value was 13.6% and negative predictive value was 93.8%. Overall, the p16INK4a positivity with the selected 9 U/mL cut-off level was 828 (78.6%) women; in comparison, biopsy-proven CIN2+ was found in only 127 (12%) women.	p16(INK4a) ELISA did not perform well as a screening test for CIN2+ detection among HIV-infected women due to low specificity. Our study contributes to the ongoing search for a more specific alternative to HPV testing for CIN2+ detection.	Low
Akinwuntan et al, 2008	To assess the correlation between cytology and VIA in HIV-positive women	205 consenting HIV-seropositive Women; 17-60 years	Nigeria	Pap smear VIA	Observational study without a control group	Sensitivity, specificity, PPV, NPV and diagnostic accuracy of Pap smear and VIA	The sensitivity of VIA was 76.0% (95% CI 52.0 – 91.0); specificity 83.0% (95% CI 77.0 – 88.0); positive predictive value 34.0% (95% CI 21.0 – 49.0). The sensitivity of Pap smear was 57.0% (95% CI 34.0 – 77.0), specificity of 95.0% (95% CI 90.0 – 97.0), and positive predictive value of 55.0% (95% CI 33.0 – 75.0).	In HIV-seropositive women, the sensitivity of VIA is 76.0%, making it a useful screening test for pre-invasive lesion of the cervix in low	Moderate

							Diagnostic accuracy of VIA is 82.0% (95% CI, 76.0-87.0) and for Pap smear is 91.0% (95% CI, 86.0-98.0)	resource settings but not a diagnostic tool.	
Firnhaber et al, 2013	To compare the sensitivity and specificity of conventional Pap smear screening to that of HPV DNA and VIA testing for detection of histologically confirmed high-grade CIN2+ in HIV-infected women	1,202 HIV-infected women; 18-65 years	South Africa	Pap smear, VIA and HPV DNA test using HC2	Observational study without a control group	Sensitivity and specificity of Pap smear, HPV DNA test and VIA	VIA and HPV were positive in 45% and 61% of women respectively. Estimated sensitivity/specificity for HPV, Pap smear and VIA for CIN 2+ was 92%/51.4%, 75.8%/83.4% and 65.4/68.5% (nurse reading), respectively. Sensitivities were similar, and specificities appeared significantly lower for the HPV test, cytology and VIA among women with CD4 counts ≤200 cells/mm(3) as compared to CD4 counts >350 cells/mm(3)	Although HPV was the most sensitive screening method for detecting CIN 2+, it was less specific than conventional cytology and VIA with digital imaging review. Screening programmes may need to be individualized in context of the resources and capacity in each area.	Moderate
Chibwesha et al, 2016	To determine the clinical performance of VIA, digital cervicography (DC), Xpert HPV, and OncoE6 for cervical cancer screening in an HIV-infected population.	200 HIV-infected women; >=18 years	Zambia	VIA, DC, Xpert HPV, and OncoE6	Observational study without a control group	Sensitivity and specificity of VIA, DC, Xpert HPV and OncoE6	Of the 200 women, 15% were screen positive by VIA, 20% by DC, 47% by Xpert HPV, and 6% by OncoE6. Using a CIN2+ threshold, the sensitivity and specificity of VIA was 48% (95% confidence interval [CI]: 30-67%) and 92% (95% CI: 86-95%), respectively. Similarly, the sensitivity and specificity of DC was 59% (95% CI: 41-76%) and 88% (95% CI: 82-93%). The sensitivity and specificity of Xpert HPV was 88% (95% CI: 71-97%), and 60% (95% CI: 52-68%). Finally, the sensitivity and specificity of OncoE6 was 31% (95% CI: 16-50%) and 99% (95% CI: 97-100%).	VIA and DC displayed moderate sensitivity and high specificity. Xpert HPV performed equivalently to currently approved HPV DNA tests, with high sensitivity and moderate specificity. OncoE6 displayed excellent specificity but low sensitivity. These results confirm an important role for VIA, DC, and Xpert HPV in screen-and-treat cervical cancer prevention in low-	Low

								and middle-income countries, such as Zambia	
Adamson et al, 2015	To (1) compare the test positivity between the two collection methods, (2) assess the accuracy and agreement of self-collected tampons compared to clinician-collected specimens for hrHPV mRNA testing, and (3) assess the acceptability of the self-collected tampon method.	325 HIV-infected women; >=25 years	South Africa	HrHPV messenger-RNA (mRNA) test	Observational study without a control group	Sensitivity and specificity of hrHPV mRNA test	Over 90% of women reported no difficulties self-collecting specimens and 82% were willing to perform the tampon-collection at home. Based on clinician-collection specimens, the prevalence of hrHPV mRNA in our study population was 36.7% (95% CI: 31.4%– 42.0%). There was no difference in test positivity between clinician-collection, 36.7%, and tampon collection, 43.5% (p-value = 0.08). Using clinician-collection as the reference test, the sensitivity and specificity for hrHPV mRNA of tampon-collection were 77.4% (95% CI: 69.8–85.0%) and 77.8% (95% CI: 71.9–83.6%), respectively.	Tampon-based self-collection is acceptable to women and has similar hrHPV mRNA positivity rates as clinician-collection, but has reduced sensitivity and specificity compared to clinician-collection.	Moderate
Segondy et al, 2016	To evaluate the performance of careHPV for detecting CIN2+ among women living with HIV-1 in Burkina Faso and South Africa	1052 HIV-1-seropositive women; 25-50 years	South Africa and Burkina Faso	careHPV assay INNO-LiPA	Observational study without a control group	Sensitivity, specificity, positive and negative predictive values of careHPV assay	Overall, 45.1% of women had a positive careHPV test (46.5% in BF, 43.8% in SA). The careHPV positivity rate increased with the grade of cytological lesions. Sensitivity and specificity of careHPV for the diagnosis of CIN2+ (n=60, both countries combined) were 93.3% (95% confidence interval (CI): 83.8-98.2) and 57.9% (95% CI: 54.5-61.2), respectively. Specificity increased with CD4 count. careHPV had a similar clinical sensitivity but higher specificity than the INNO-LiPA assay for detection of CIN2+	Results suggest that careHPV testing is a reliable tool for cervical cancer screening in HIV-1-infected women in sub-Saharan Africa.	Moderate

Bateman et al, 2014	To assess the clinical performance of DC, as well as cytology in HIV-infected women	303 women; 20-45 years	Zambia	DC Pap smear	Observational study without a control group	Clinical performance of each screening test to detect cervical lesions on histopathology.	The sensitivity of DC for identifying CIN2+ was 84% (95% CI: 72% – 91%) and the specificity was 58% (95% CI: 52% – 64%) (Table 2). The sensitivity estimates of cytology for identifying CIN2+ were as follows: HSIL+, 61% (95% CI: 48% – 72%); LSIL+, 90% (95% CI: 80% – 95%); ASC-US+, 100% (95% CI: 94% – 100%). The specificity estimates of cytology for identifying CIN2+ were: HSIL+, 58% (95% CI: 52% – 64%); LSIL+, 35% (95% CI: 29% – 41%); ASC-US+, 13% (95% CI: 10% – 18%). The PPVs were low (23% – 33%) for both tests, while the NPVs were correspondingly high (86% – 100%). A similar pattern of results was observed at the CIN3+ diagnostic threshold on histopathology (Table2).	Digital cervicography appears to be as good as cytology in HIV-infected women.	Moderate

Appendix 16: Table of clinical performance of different cervical cancer screening methods in detecting CIN2+

Author & year of publication	Screening method/tool	HIV-infected				HIV-negative			
		Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
Bansil et al, 2015	VIA	77.1 (59.9-89.6)	47.3 (40.8-53.8)	17.8 (12.0-24.8)	93.3 (87.3-97.1)	93.8 (69.8-99.8)	60.5 (57.3–63.7)	3.9 (2.2–6.4)	99.8(99.0–100.0)
Chung et al, 2013	VIA	62.7 (53.4–71.2)	65.9 (60.7–70.7)	37.1 (30.5–44.2)	84.6 (79.8–88.5)				
Dartell et al, 2014	VIA	50.0 (31.5-68.5)	90.5 (87.2-93.8)	32.6	95.2	22.9 (14.5-31.3)	97.2 (96.7-97.8)	21.6	97.5
Huchko et al, 2015	VIA	84.0 (64.0–95.5)	78.6 (73.5–83.1)	24.7 (16.0–35.3)	98.3 (95.8–99.5)				
Joshi et al, 2013	VIA	83.6 (71.2–92.2)	88.8 (86.7–90.6)	27.7 (21.1–35.2)	99.1 (98.2–99.6)				
Kuhn et al, 2010	VIA	63.9 (46.2-79.2)	73.5 (67.4-78.8)	27.5 (17.8-37.3)	90.9 (85.8-96.0)	47.8 (35.7-60.2)	80.3 (78.2-82.2)	9.6 (6.5-12.7)	96.7 (95.6-97.8)
Mabeya et al, 2012	VIA	69.6	51.0	38.6	79.1				
Sahasrabuddhe et al, 2012	VIA	80.0 (66.3–90.0)	82.6 (77.4–87.1)	47.6 (36.6–58.9)	95.4 (91.8–97.8)				
Akinwuntan et al, 2008	VIA	76.0 (52.0-91.0)	83.0 (77.0-88.0)	34.0 (21.0-49.0)	97.0 (92.0-99.0)				
Firnhaber et al, 2016	VIA	65.4 (59.7-71.1)	68.5 (65.3-71.7)						
Chibwesha et al, 2016	VIA	48.0 (30.0-67.0)	92.0 (86.0-95.0)	52.0 (33.0-71.0)	91.0 (85.0-95.0)				

Huchko et al, 2015	VILI	84.2 (68.7–94.0)	76.4 (71.2–81.3)	31.7 (22.8–41.7)	97.4 (94.4–99.0)				
Joshi et al, 2013	VILI	89.1 (77.8–95.9)	89.3 (87.3–91.1)	30.1 (23.1–37.7)	99.4 (98.6–99.8)				
Chibwesha et al, 2016	DC	59.0 (41.0-76.0)	88.0 (82.0-93.0)	49.0 (32.0-65.0)	92.0 (87.0-96.0)				
Bateman et al, 2014	DC	84.0 (72.0-91.0)	58.0 (52.0-64.0)	33.0 (26.0-41.0)	93.0 (88.0-96.0)				
Joshi et al, 2013	Pap smear	63.3 (48.3–76.6)	94.5 (92.9–95.8)	35.2 (25.3–46.1)	98.2 (97.2–98.9)				
Chung et al, 2013	Pap smear	71.8 (62.8–79.4)	97.1 (94.7–98.4)	88.8 (80.5–93.8)	91.5 (88.2–93.9)				
Mabeya et al, 2013	Pap smear	52.5	66.3	39.7	76.8				
Sahasrabuddhe et al, 2012	Pap smear	60.5 (44.4–75.0)	64.6 (57.9–70.8)	24.8 (16.9–34.1)	89.4 (83.6–93.7)				
Akinwuntan et al, 2008	Pap smear	57.0 (34.0-77.0)	95.0 (90.0-97.0)	55.0 (33.0-75.0)	95.0 (91.0-98.0)				
Firnhaber et al, 2013	Pap smear	75.8 (70.8-80.8)	83.4 (80.9-85.9)						
Bateman et al, 2014	Pap smear	61.0 (48.0-72.0)	58.0 (52.0-64.0)	27.0 (20.0-35.0)	86.0 (79.0-90.0)				
Michelow et al, 2016	Cellslide(®)automated liquid-based cytology	76.0 (64.8–85.1)	91.0 (87.0–94.2)	70.4 (59.2–80.0)	93.1 (89.4–95.9)				

Bansil et al, 2015	Vaginal careHPV	80.0 (63.1–91.6)	59.9 (53.4–66.2)	22.8 (15.7–31.2)	95.3 (90.6–98.1)	75.0 (47.6–92.7)	81.9 (79.3–84.4)	6.7 (3.5–11.4)	99.5 (98.7–99.9)
Bansil et al, 2015	Cervical careHPV	94.3 (80.8–99.3)	62.4 (55.9–68.6)	27.0 (19.4–35.8)	98.7 (95.3–99.8)	81.3 (54.4–96.0)	80.9 (78.2–83.3)	6.8 (3.7–11.4)	99.6 (98.8–99.9)
Obiri-Yeboah et al, 2017	CareHPV	87.5 (47.3–99.7)	52.1 (44.7–59.5)	7.2 (3.0–14.3)	99.0 (94.5–100.0)				
Segondy et al, 2016	CareHPV	93.3 (83.8-98.2)	57.9 (54.5-61.2)						
Chung et al, 2013	HPV DNA test	83.6 (75.6–89.4)	55.7 (50.4–60.9)	37.7 (31.9–43.9)	91.4 (86.8–94.5)				
Dartell et al, 2014	HR HPV	100.0	58.2 (52.6.63.7)	17.9	100.0	92.7 (87.5-97.9)	85.3 (84.0-86.6)	17.2	99.7
Joshi et al, 2013	HC2 test	94.6 (84.9–98.9)	77.4 (74.8–79.9)	17.8 (13.6–22.6)	99.6 (99.0–99.9)				
Ngou et al, 2015	HC2	88.8	55.2	24.7	96.7				
Ngou et al, 2015	INNO-LiPA	92.5	35.1	19.1	96.6				
Obiri-Yeboah et al, 2017	Anyplex II HPV 28	87.5 (47.3–99.7)	38.8 (31.8–46.2)	5.7 (2.3–11.5)	98.6 (92.7–100.0)				
Firnhaber et al, 2016	HC2	91.9 (88.5-95.3)	51.4 (48.0-54.8)						
Chibwesha et al, 2016	Xpert HPV	88.0 (71.0-97.0)	60.0 (52.0-86.0)	30.0 (21.0-40.0)	96.0 (90.0-99.0)				
Chibwesha et al, 2016	OncoE6	31.0 (16.0-50.0)	99.0 (97.0-100)	91.0 (59-100)	88.0 (83.0-93.0)				
Segondy et al, 2016	INNO-LiPA	96.7 (88.5-99.6)	32.0 (29.0-35.2)						
Kuhn et al, 2010	HPV DNA	94.4 (81.3-99.3)	64.4 (58.0-70.3)	29.9 (21.3-38.6)	97.2 (87.0-99.4)	87.0 (76.7-93.9)	87.0 (85.2-88.6)	22.7(17.6-27.9)	99.0 (97.9-99.5)

Wu et al, 2016	P16INK4a cut-off level=9 U/mL (%)	89.0	22.9	13.6	93.8				
Chung et al, 2013	VIA+HPV test	58.2 (48.8–67.0)	83.7 (79.4–87.2)	53.3 (44.4–62.0)	86.2 (82.1–89.5)				
Chung et al, 2013	VIA+Pap smear	50.9 (41.7–60.1)	99.1 (97.5–99.7)	94.9 (86.1–98.3)	86.3 (82.5–89.3)				
Chung et al, 2013	HPV+Pap smear	62.7 (53.4–71.2)	98.5 (96.6–99.4)	93.2 (85.1–97.1)	89.2 (85.7–91.9)				
Joshi et al, 2013	VIA and VILI	81.8 (69.1–90.9)	93.2 (91.5–94.6)						
Joshi et al, 2013	HC2 and VIA	80.0 (67.0–89.6)	96.0 (94.6–97.1)						
Joshi et al, 2013	HC2 and VILI	83.6 (71.2–92.2)	96.9 (95.7–97.9)						
Joshi et al, 2013	HC2 and VIA/VILI	85.5 (73.3–93.5)	95.3 (93.9–96.5)						
Joshi et al, 2013	VIA and cytology	57.1 (42.2–71.2)	98.8 (98.0–99.4)						
Joshi et al, 2013	VILI and cytology	55.1 (40.2–69.3)	99.6 (99.0–99.9)						
Joshi et al, 2013	HC2 and cytology	63.3 (48.3–76.6)	96.6 (95.3–97.6)						

Appendix 17: Table of evidence of the treatment systematic review

First author & publication year	Study type	Purpose	Population & age	Country	Stage of cancer	Treatment method	Outcome(s)	Results	Authors' Conclusions	Quality score
Simonds et al, 2012	Retrospective cohort study	To compare the clinical characteristics, radiation and chemotherapy treatments, outcomes in a cohort of HIV-positive and –negative women with cervical cancer	59 HIV-positive (median age 41 years) and 324 HIV-negative (median age of 50 years) patients	South Africa	IBi - IIIB	Radiation and chemotherapy	Chemotherapy cycles, response at time of brachytherapy and six-week follow-up	88.1% of HIV-positive patients presented with IIIB disease compared to 65.7% of HIV-negative patients (p=0.009). 79.7% HIV-positive and 89.8% HIV-negative patients completed Radiation dose of 68Gy EBRT and HDR brachytherapy (p=0.03). For concurrent chemotherapy, 53.1% HIV-positive and 74.6% HIV-negative patients completed four or more weekly cycles of platinum-based treatment. At 6 weeks, poor response was associated with stage IIIB disease (OR=2.39, 95% CI 1.45-3.96) and receiving less than 68Gy EQD_2 radiation(OR=3.14, 95%CI 1.24-794).	Good medical care of HIV-positive patients can enable patients to complete treatment for locally advanced cervical cancer and might improve response to treatment.	Moderate
Shrivastava et al, 2005	Retrospective review	To determine the effect of radiotherapy in HIV seropositive cervical cancer patients, tumour response and toxicity and compliance of patients to the treatment.	42 HIV seropositive patients, mean age of 41 years	India	IIIB - IVA	Radiotherapy	Age and symptoms of presentation, clinical stage, response, compliance and tolerance to radiotherapy	All patients presented with the symptoms of cervical disease. Of these patients 31(74%) patients had 'Karnofsky Performance Scale' (KPS) more than 80%. Twenty-one (50%) of the patients were of Stage IIIb–IVa. Thirty-two (76%) were started on radiotherapy with radical intent. Compliance to radiotherapy was poor with 24% patients discontinuing after few fractions of	Radiotherapy is effective in this set of patients. Palliative fractionation schedules are effective for patients with poor performance status and locally advanced	Low

								radiotherapy. Seven (17%) patients were given palliative radiotherapy. Twenty-two patients completed prescribed radical radiotherapy and 50% of these achieved complete response. Grade III–IV acute gastrointestinal toxicity was seen in 14% of the patients, and grade III acute skin toxicity was seen in 27% of patients, leading to treatment delays. There was good relief of symptoms in patients treated with palliative intent.	cancers in relieving the symptoms related to carcinoma cervix. An emphasis should be given to the increased acute mucosal and skin toxicity and to improving compliance and clinical outcome of these patients.	
Gichangi et al, 2006	Prospective cohort study	To determine the impact of HIV infection on acute morbidity and pelvic tumour control following external beam radiotherapy (EBRT) for cervical cancer	218 patients, 20% of them HIV-positive	Kenya		Radiotherapy	Acute treatment toxicity and pelvic tumour control	Overall, 53.4% of the patients had radiation-related acute toxicity (grade 3-4). HIV infection was associated with a 7-fold higher risk of multisystem toxicity: skin, gastrointestinal tract (GIT) and genitourinary tract (GUT) systems. It was also an independent risk factor for treatment interruptions (adjusted relative risk 2.2). About 19% of the patients had residual tumour at 4 and 7 months post-EBRT. HIV infection was independently and significantly associated with 6-fold higher risk of residual tumour post-EBRT. The hazard ratio of having residual tumour after initial	HIV is associated with increased risk of multisystem radiation-related toxicity; treatment interruptions and pelvic failure (residual tumour) following EBRT. HIV infection is an adverse prognostic factor for	Moderate

								EBRT was 3.1-times larger for HIV-positive than for HIV-negative patients (P = 0.014).	outcome of cervical cancer treatment.	
Mdletshe et al, 2016	Prospective quantitative comparative study	To evaluate in detail treatment response, its toxicities and compliance of HIV-positive women to radical combination therapy (radiotherapy with chemotherapy)	55 HIV-positive (median age of 40 years) and 55 HIV-negative (median age of 55 years) patients with performanc e status ECOG I & II	Zambia	IB_2 - IIIB	Combination of radiotherapy and chemotherapy given concurrently	Acute reactions to radical chemo-radiation and toxicity	All participants completed EBR and HDR as prescribed. Average EBR dose delivered was 48Gy and the difference in dose received was significant with regard to HIV status (p=0.022). 58% of HIV-positive were treated with 6.5Gy x 4 brachytherapy fractions as compared to 58% HIV-negative patients treated with 8Gy x 3 fractions. There were no statistically significant differences in toxicity between HIV-positive and –negative patients with regard to skin, GIT system, GU system and Haemopoietic system.	Radical chemo-radiation in conventional doses was safely tolerated by a well-selected cervical cancer HIV-positive group on HAART and could be considered suitable for similar patients.	Moderate
Boupaijit & Suprasert, 2016	Retrospective study	To evaluate the survival outcomes of chemotherapy and the prognostic factors in this setting	173 patients (mean age of 50.9 year), with 4.1% of them HIV-positive	Thailand	IVB	Chemotherapy	Survival outcomes and prognostic factors	Median overall survival of all studied patients was 13.2 months. Only a recurrence free interval of less than 12 months was an independent prognostic factor for survival outcome	Chemotherap y treatment for advanced and recurrent cervical cancer patients showed modest efficacy with a shorter recurrence free survival less than 12	Moderate

									months as a significant poor prognosis factor	
Ferreira et al, 2017	Cohort study	To assess mortality, treatment response, and relapse among HIV-infected and HIV-uninfected women with cervical cancer in Rio de Janeiro, Brazil	87 HIV-infected and 336 HIV-uninfected women with cervical cancer	Brazil	IA/IB1, IB2/II, III, IVA/IVB	28% treated with surgery, 23% with radiation, 30% with chemo-radiation, & 36% received additional brachytherapy	Mortality, treatment response and relapse	70% HIV-infected women & 76% HIV-uninfected women completed recommended treatment. 58t HIV-infected and 176 HIV-uninfected women died. Among HIV-infected women, overall mortality was 324 per 1000 person-years, with 82% of deaths due to cancer. Among HIV-uninfected women, overall mortality was 209 per 1000 person-years, with 93% of deaths from cancer. Among 222 patients treated with radiotherapy, HIV-infected had similar response rates to initial cancer therapy as HIV-uninfected women (HR 0.98, 95%CI 0.58–1.66). However, among women who were treated and had a complete response, HIV was associated with elevated risk of subsequent relapse (HR 3.60, 95%CI 1.86–6.98, adjusted for clinical stage)	HIV infection was not associated with initial treatment response or early mortality, but relapse after attaining a complete response and late mortality were increased in those with HIV. There is a role for an intact immune system in control of residual tumour burden among treated cervical cancer patients	Moderate
Moodley, 2017	Case studies	To present radical hysterectomy experience to inform	18-year-old nulliparous, 36-year-old primiparous, and 39-	South Africa	Differentiated squamous cell carcino	Surgery (radical hysterectomy)	Management outcomes after radical hysterectomy	All three made uneventful postoperative recoveries and all vaginal vault cytologic smears have been negative. 18-year-old is well 6 years	With reasonable levels of immunosuppr	Low

		management of early-stage invasive cervical cancer	year-old para 2 HIV-positive women		ma (LVSI),			postsurgery as are the 36- and 39-year-olds at 3 years follow-up visits. The 39-year-old patient needed ureteric re-implantation due to ureteric stricture, which could occur as a recognized complication even in HIV Non-infected patients.	ession, management of HIV-positive women with early cervical cancer with radical hysterectomy can produce reasonable outcomes and survival.	
Kietpeerakool et al, 2006	Retrospective cohort study	To evaluate the treatment outcomes and complications in human immunodeficiency virus (HIV)–infected women undergoing loop electrosurgical excision procedure (LEEP) for cervical neoplasia	60 HIV-infected (mean age of 35.9 years) and 61 HIV-negative (mean age of 40.1 years) women with cervical neoplasia	Thailand	LSIL - HSIL	LEEP	LEEP treatment outcomes and complications in HIV-positive women	97.1% and 88% of HIV-positive women were disease-free at 6 and 12 months, respectively after LEEP. 1.7% had severe intraoperative haemorrhage, 5% had early and late postoperative haemorrhage, 11.7% had localised infection of the cervix and 3.3% developed cervical stenosis at 6 months after LEEP. No significant difference in overall complications (p=0.24) between HIV-positive and –negative patients.	LEEP appears to be safe and effective in HIV-infected women.	Moderate
Firnhaber et al, 2017	Randomised controlled trial	To compare cervical cryotherapy to observation in HIV-infected women with	202 HIV-positive women (median age of 37.9	South Africa	CIN1	Cryotherapy	CIN2/3 by histology at month 12. Regression of cervical histology to no	CIN2/3 at month 12, occurred in 2 of 99 (2%) women in the cryotherapy arm as compared with 15 of 103 (15%) women in the no treatment arm [86% risk	Treating CIN1 with cryotherapy reduces progression to CIN2/3. The	High

		CIN1 on histology	years) with CIN1				evidence of NILM	reduction, 95% confidence interval (CI): 61% to 97%; P = 0.0016]. No cervical cancers in both arms. Forty of 99 (40%) women in the cryotherapy group experienced regression as compared 14 of 103 (14%) women in the no treatment group, (69% reduced regression, 95% CI: 58% to 83%, P, 0.0001).	benefit was exclusively among those with hrHPV. Cryotherapy was safe in this population with no serious adverse events.	
Woo et al, 2011	Prospective cohort study	To estimate the safety, tolerability, and acceptability of loop electrosurgical excision procedure (LEEP) for cervical intraepithelial neoplasia (CIN 2/3) in HIV-positive women	180 HIV-positive women	Kenya	CIN2/3	LEEP	Safety, tolerability and acceptability of LEEP after 4 weeks post-procedure	179 (99%) reported "very mild" to mild symptoms, while 1 (n=1%) participant described the symptoms as moderate. Mean CD4+ count was significantly higher among women who reported any symptoms compared to women who reported no symptoms post LEEP (419 cells/mm3 vs. 349 cells/mm3, $p < 0.05$) Only 16% (CI 11–22%, n=29) of women reported early resumption of intercourse prior to their 4-week follow-up visit	LEEP performed by clinical officers was well-accepted by HIV positive women and appears safe, resulting in minimal side effects, even among women with early resumption of intercourse	Moderate
Kietpeerakool et al, 2008	Prospective study	To assess outcome in HIV-positive women undergoing the loop electrosurgical excision procedure (LEEP)	70 HIV-positive (mean age of 37.5) and 719 HIV-negative (mean age 45.8) women.	Thailand	CIN1/2/3, IA1-IB1	LEEP	Safety of LEEP among HIV-positive patients	HIV infection was not significantly associated with the incidence of LEEP complications (adjusted odds ratio, 0.41; 95% CI, 0.15–1.15; P=0.10). There were no statistically significant differences in operative time, size of excised specimens, incidence	LEEP is safe in HIV-infected women with cervical neoplasia treated in outpatient settings; and when technically	Moderate

								of 2 or more passes of the loop, or use of Monsel paste between the 2 groups. There was a higher prevalence of LEEP margin involvement in the HIV-positive than in the HIV-negative group (60.0% vs 49.4%).	possible, a repeat intervention is safe, with an acceptable success rate, even though HIV-infected women have a higher risk of resection margin involvement.	
Smith et al, 2017	Randomised controlled trial	To identify effective treatment methods for high-grade cervical precursors among HIV-seropositive women by comparing the difference in the efficacy of loop electrosurgical excision procedure vs cryotherapy for the treatment of high-grade cervical intraepithelial neoplasia (grade ≥2)	166 HIV-seropositive women aged 18-65 years	South Africa	CIN2+	Cryotherapy vs LEEP	Efficacy of LEEP and cryotherapy	Cumulative cervical intraepithelial neoplasia grade ≥2 incidence was higher for cryotherapy (24.3%; 95% confidence interval, 16.1-35.8) than LEEP at 6 months (10.8%; 95% confidence interval, 5.7-19.8) (P = .02), although by 12 months, the difference was not significant (27.2%; 95% confidence interval, 18.5-38.9 vs 18.5%; 95% confidence interval, 11.6-28.8, P = .21). Cumulative cervical intraepithelial neoplasia grade ≥1 incidence for cryotherapy (89.2%; 95% confidence interval, 80.9-94.9) did not differ from LEEP (78.3%; 95% confidence interval, 68.9-86.4) at 6 months (P = .06); cumulative cervical intraepithelial neoplasia grade ≥1 incidence by 12 months was higher for cryotherapy (98.5%; 95%	Both treatments appeared effective in reducing cervical intraepithelial neoplasia grade ≥2 by >70% by 12 months. The difference in cumulative cervical intraepithelial neoplasia grade ≥2 incidence between the 2 treatment methods by 12 months was not statistically significant. Relatively high cervical	High

								confidence interval, 92.7-99.8) than LEEP (89.8%; 95% confidence interval, 82.1-95.2) (P = .02). Cumulative high-grade cytology incidence was higher for cryotherapy (41.9%) than LEEP at 6 months (18.1%, P < .01) and 12 months (44.8% vs 19.4%, P < .001). Cumulative incidence of low-grade cytology or greater in cryotherapy (90.5%) did not differ from LEEP at 6 months (80.7%, P = .08); by 12 months, cumulative incidence of low-grade cytology or greater was higher in cryotherapy (100%) than LEEP (94.8%, P = .03).	intraepithelial neoplasia grade ≥2 recurrence rates, indicating treatment failure, were observed in both treatment arms by 12 months. A different treatment protocol should be considered to optimally treat cervical intraepithelial neoplasia grade ≥2 in HIV-seropositive women	

Appendix 18: Ethical clearances for the studies

Amendment with the new Title.

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.
- FWA 00002567, Approved dd 22 May 2002 and Expires 03/20/2022.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 03/14/2020.

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

26/04/2018

Approval Certificate
Amendment
(to be read in conjunction with the main approval certificate)

Ethics Reference No: 146/2016

Title: The epidemiology and knowledge of cervical cancer in Zimbabwe.

Dear Witness Mapanga

The **Amendment** as described in your documents specified in your cover letter dated 15/03/2018 received on 15/03/2018 was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 25/04/2018.

Please note the following about your ethics amendment:
- Please remember to use your protocol number (**146/2016**) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committe may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics amendment is subject to the following:
- The ethics approval is conditional on the receipt of **6 monthly written Progress Reports**, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted **as** an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

Dr R Sommers; MBChB; MMed (Int); MPharMed; PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health).

012 356 3084 deepeka.behari@up.ac.za / fhsethics@up.ac.za http://www.up.ac.za/healthethics
Private Bag X323, Arcadia, 0007 - Tswelopele Building, Level 4, Room 60 / 61, 31 Bophelo Road, Gezina, Pretoria

Original with the old title

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.
- FWA 00002567, Approved dd 22 May 2002 and Expires 20 Oct 2016.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 22/04/2017.

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

14/06/2016

Approval Certificate
New Application

Ethics Reference No.: 146/2016

Title: The epidemiology and knowledge about/concerning cervical cancer in Zimbabwe

Dear Witness Mapanga

The **New Application** as supported by documents specified in your cover letter dated 12/04/2016 for your research received on the 12/04/2016, was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 140/06/2016.

Please note the following about your ethics approval:
- Ethics Approval is valid for 2 years
- Please remember to use your protocol number (**146/2016**) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:
- The ethics approval is conditional on the receipt of **6 monthly written Progress Reports**, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

Dr R Sommers: MBChB; MMed (Int); MPharMed,PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

☎ 012 356 3084 deepeka.behari@up.ac.za http://www.up.ac.za/healthethics
✉ Private Bag X323, Arcadia, 0007 Tswelopele Building, Level 4-60, Gezina, Pretoria

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences
School of Health Systems and Public Health
Biostatistics and Epidemiology Track

14 September 2017

The Dean of Students
University of Zimbabwe

Re: Request for permission to carry out PhD research study at University of Zimbabwe

I am a student at the School of Health Systems and Public Health, University of Pretoria, studying for a PhD Epidemiology degree. It is a requirement of the university that all students must carry out research studies in partial fulfilment of the degree's requirements. I am therefore kindly seeking for permission to carry out research at the University of Zimbabwe on the "**The epidemiology and knowledge about/concerning cervical cancer in Zimbabwe**". My supervisors are Professor Shingairai Feresu and Professor Tsungai Chipato.

Attached are letters confirming my ethical clearance from the University of Pretoria, Medical Research Council of Zimbabwe and the Ministry of Higher and Tertiary Education. I have also attached my study summary, data collection instrument and consent form.

Should you need more information, do not hesitate to contact me at cell +263 775 142 253 or Professor Feresu at +27 60475 1881 or Professor Chipato at +263 773 177 045.

Yours faithfully,

Witness Mapanga, PhD Student
Department of Epidemiology & Biostatistics Track
School of Health Systems and Public Health
University of Pretoria
5-10 H.W. Snyman Building
Pretoria, South Africa
E-mail: witnessmapanga@yahoo.co.uk
Website: http://shsph.up.ac.za

UNIVERSITY OF ZIMBABWE
STUDENTS AFFAIRS DIVISION
2017 -09- 22
DEAN OF STUDENTS

Approved
21/9/2017

School of Health Systems and Public Health
University of Pretoria
Private Bag X323
Pretoria South Africa 0001

Tel Number +27 12 354 1472
Fax Number +27 12 354 2071

Email address shsph@up.ac.za
http://shsph.up.ac.za
www.up.ac.za

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences
School of Health Systems and Public Health
Biostatistics and Epidemiology Track

15 September 2017

The Registrar
Midlands State University

Re: Request for permission to carry out PhD research study at Midlands State University

I am a student at the School of Health Systems and Public Health, University of Pretoria, studying for a PhD Epidemiology degree. It is a requirement of the university that all students must carry out research studies in partial fulfilment of the degree's requirements. I am therefore kindly seeking for permission to carry out research at Midlands State University on the **"The epidemiology and knowledge about/concerning cervical cancer in Zimbabwe".** My supervisors are Professor Shingairai Feresu and Professor Tsungai Chipato.

Attached are letters confirming my ethical clearance from the University of Pretoria, Medical Research Council of Zimbabwe and the Ministry of Higher and Tertiary Education. I have also attached my study summary, data collection instrument and consent form.

Should you need more information, do not hesitate to contact me at cell +263 775 142 253 or Professor Feresu at +27 60475 1881 or Professor Chipato at +263 773 177 045.

Yours faithfully,

Witness Mapanga, PhD Student
Department of Epidemiology & Biostatistics Track
School of Health Systems and Public Health
University of Pretoria
5-10 H.W. Snyman Building
Pretoria, South Africa
E-mail: witnessmapanga@yahoo.co.uk
Website: http://shsph.up.ac.za

Approved

MIDLANDS STATE UNIVERSITY
FACULTY OF ARTS
4 OCT 2017
SENIOR ASSISTANT REGISTRAR
PRIVATE BAG [illegible], GWERU
ZIMBABWE TEL/FAX: 054-260068

02/10/17

School of Health Systems and Public Health
University of Pretoria
Private Bag X323
Pretoria South Africa 0001

Tel Number +27 12 354 1472
Fax Number +27 12 354 2071

Email address shsph@up.ac.za
http://shsph.up.ac.za
www.up.ac.za

AFRICA UNIVERSITY
"Investing in Africa's Future"

REGISTRAR'S OFFICE

A UNITED METHODIST - RELATED INSTITUTION

P.O. BOX 1320, MUTARE, ZIMBABWE - TEL.: (263-20) 60075/60026/61618 - FAX: (263-20) 61785 - E-MAIL: registrar@africau.edu

15 September, 2017

Mr Witness Mapanga, PhD Student
Department of Epidemiology & Biostatistics Track
Scholl of Health Systems and Pubic Health
University of Pretoria
5-10 H W Snyman Building
Pretoria
SOUTH AFRICA

Dear Mr Mapanga

E-MAIL : witnessmapanga@yahoo.co.uk;

PERMISSION TO CARRY OUT RESEARCH

We have pleasure to inform you that your application to carry out research at Africa University has been approved in line with the Africa University Research Ethics Committee (AUREC) terms and conditions.

Letter from AUREC dated 17 August, 2017 refers.

We wish you success with your research.

Yours faithfully

H NJONGA (MR)
REGISTRAR

cc Interim Deputy Vice Chancellor
Dean, College of Health, Agriculture & Natural Sciences
Mr Miti – AUREC Officer

From the Office of the Secretary for Higher and Tertiary Education, Science and Technology Development

All official communications should be addressed to:
"The Secretary"

Telephones: 795891-5, 796441-9, 730055-9
Fax Number: 733070
Telegraphic address: "EDUCATION"

ZIMBABWE

Reference:

MINISTRY OF HIGHER AND TERTIARY EDUCATION, SCIENCE AND TECHNOLOGY DEVELOPMENT
P. BAG CY 7732
CAUSEWAY

02 November 2016

School of Health Systems and Public Health
University of Pretoria
5-10 H. W. Snyman Building
Pretoria
SOUTH AFRICA

Department of Epidemiology & Biostatistics Track

Dear Mr Witness Mapanga

RE: REQUEST OF AUTHORITY TO CARRY OUT A RESEARCH ON "THE EPIDEMIOLOGY AND KNOWLEDGE ABOUT/CONCERNING CERVICAL CANCER IN ZIMBABWE": MINISTRY OF HIGHER AND TERTIARY EDUCATION, SCIENCE AND TECHNOLOGY DEVELOPMENT

Reference is made to your, letter in which you requested for permission to carry out a research on **"The Epidemiology and knowledge about/concerning cervical cancer in Zimbabwe".**

Accordingly, please be advised that the Head of Ministry has granted permission for you to carry out the research.

It is hoped that your research will benefit the Ministry and it would be appreciated if you could supply the office of the Permanent Secretary with a final copy of your study, as the findings would be relevant to the Ministry's strategic planning process.

Maedze F. (Mrs)
A/Director – Human Resources
For: PERMANENT SECRETARY

MIN. OF HIGHER & TERTIARY EDU. SCIENCE & TECHNOLOGY 02 HUMAN RESOURCES 02
2016 -12- 02
P. BAG 7732, CAUSEWAY ZIMBABWE

All communications should be addressed to
"The Secretary for Primary and Secondary Education"
Telephone: 799914 and 705153
Telegraphic address : "EDUCATION"
Fax: 791023

ZIMBABWE

Reference: C/426/3 Harare, Masvingo,
MinistryP of Primary and Secondary Education
P.O Box CY 121
Causeway
Harare
Zimbabwe

2 August 2016

Witness Mapanga
Department of Epidemiology and Biostatistics Track
School of Health Systems and Public Health
University of Pretoria
5-10 H.W. Synman Building
Pretoria
South Africa

RE: PERMISSION TO CARRY OUT RESEARCH IN HARARE PROVINCE, SCHOOLS.

Reference is made to your application to carry out a research in above mentioned provinces, with schools on next page on the research title:

"THE EPIDEMIOLOGY AND KNOWLEDGE ABOUT/ CONCERNING CERVICAL CANCER IN ZIMBABWE."

Permission is hereby granted. However, you are required to liaise with the Provincial Education Director Harare, who is responsible for the schools which you want to involve in your research. You should ensure that your research work does not disrupt the normal operations of the school. You are required to seek consent of the parents/guardians of all learners who will be involved in the research.

You are required to provide a copy of your presentation and a report of what transpired to the Secretary for Primary and Secondary Education by December 2016.

MIN. OF PRY. & SEC. EDUCATION
POLICY PLANNING RESEARCH
& DEVELOPMENT
02 AUG 2016
P.O. BOX CY 121, CAUSEWAY
ZIMBABWE

E. Chinyowa
Acting Director: Policy Planning, Research and Development
For: **SECRETARY FOR PRIMARY AND SECONDARY EDUCATION**
cc: PED – Harare Province

All communications should be addressed to "THE PROVINCIAL EDUCATION DIRECTOR"

Telephone : 04-339334/04-332123
E-mail :
hararemetropolitanprovince@gmail.com

ZIMBABWE

REF: G/42/1
Ministry of Primary and Secondary Education
Harare Provincial Education Office
P. O. Box CY 1343
Causeway
Zimbabwe

24 October 2017

Witness Mapanga
Department of Epidemiology and Biostatistics Track
Schools of Health systems and Public Health
University of Pretoria
5 – 10 H. W Synman Building
South Africa

RE: PERMISSION TO CARRY OUT RESEARCH IN SOME SELECTED SCHOOLS

In Harare Province schools "THE EPIDEMIOLOGY AND KNOWLEDGE ABOUT/CONCERNING CERVICAL CANCER IN ZIMBABWE)

Reference is made to your letter dated ***02 August 2017.***

Please be advised that the Provincial Education Director grants you authority to carry out your research on the above topic. You are required to supply Provincial Office with a copy of your research findings.

pp Mateyi R (EA) .....

MIN. OF PRY. & SEC. EDUCATION
DISCIPLINE SECTION
HARARE PROVINCE
24 OCT 2017
P.O. BOX CY 1343 CAUSEWAY
TEL: 04-772431/2/793146

For: Provincial Education Director
Harare Metropolitan Province

Telephone: 791792/791193
Telefax: (263) - 4 – 790715
E-mail: mrcz@mrcz.org.zw
Website: http://www.mrcz.org.zw

Medical Research Council of Zimbabwe
Josiah Tongogara / Mazoe Street
P. O. Box CY 573
Causeway
Harare

APPROVAL

REF: MRCZ/A/2135 **3 May, 2017**

Witness Mapanga
University of Pretoria
School of Health Systems and Public Health
5-10 H.W Synman Building
Pretoria

RE:- The Epidemiology And Knowledge About/Concerning Cervical Cancer In Zimbabwe

Thank you for the application for review of Research Activity that you submitted to the Medical Research Council of Zimbabwe (MRCZ). Please be advised that the Medical Research Council of Zimbabwe has **reviewed** and **approved** your application to conduct the above titled study.

This approval is based on the review and approval of the following documents that were submitted to MRCZ for review:-

1. Study Protocol
2. KAP Study - Adult Consent Form, (English, Shona and Ndebele)
3. KAP Study - Parent Consent Form, (English, Shona and Ndebele)
4. KAP Study - Assent Form (English, Shona and Ndebele)
5. Case Control Study - Consent Form, (English, Shona and Ndebele)
6. Data Extraction Form_Case Control Study, (English)
7. Questionnaire_Case Control Study, (English)
8. Questionnaire_KAP Study, (English)
9. Information Brochure_Case Control Study, (English)

- **APPROVAL NUMBER** **: MRCZ/A/2135**

This number should be used on all correspondence, consent forms and documents as appropriate.

- **TYPE OF MEETING** **: Normal review**
- **EFFECTIVE APPROVAL DATE** **: 05 May, 2017**
- **EXPIRATION DATE:-** **: 04 May, 2018**

After this date, this project may only continue upon renewal. For purposes of renewal, a progress report on a standard form obtainable from the MRCZ Offices should be submitted three months before the expiration date for continuing review.

- **SERIOUS ADVERSE EVENT REPORTING**: All serious problems having to do with subject safety must be reported to the Institutional Ethical Review Committee (IERC) as well as the MRCZ within 3 working days using standard forms obtainable from the MRCZ Offices or website.
- **MODIFICATIONS**: Prior MRCZ and IERC approval using standard forms obtainable from the MRCZ Offices is required before implementing any changes in the Protocol (including changes in the consent documents).
- **TERMINATION OF STUDY**: On termination of a study, a report has to be submitted to the MRCZ using standard forms obtainable from the MRCZ Offices or website.
- **QUESTIONS**: Please contact the MRCZ on Telephone No. (04) 791792, 791193 or by e-mail on mrcz@mrcz.org.zw

Other

- Please be reminded to send in copies of your research results for our records as well as for Health Research Database.
- You're also encouraged to submit electronic copies of your publications in peer-reviewed journals that may emanate from this study.

Yours Faithfully

.....
MRCZ SECRETARIAT
FOR CHAIRPERSON
MEDICAL RESEARCH COUNCIL OF ZIMBABWE

MEDICAL RESEARCH COUNCIL OF ZIMBABWE
APPROVED
P.O. BOX CY 573 CAUSEWAY, HARARE

PROMOTING THE ETHICAL CONDUCT OF HEALTH RESEARCH

Appendix 19: Publications based on this thesis

Mapanga et al. Systematic Reviews (2018) 7:198
https://doi.org/10.1186/s13643-018-0874-7

Systematic Reviews

SYSTEMATIC REVIEW UPDATE Open Access

Prevention of cervical cancer in HIV-seropositive women from developing countries through cervical cancer screening: a systematic review

Witness Mapanga[1,5*], Brendan Girdler-Brown[1], Shingairai A. Feresu[2], Tsungai Chipato[3] and Elvira Singh[1,4]

Abstract

Background: There is scanty or inconclusive evidence on which cervical cancer screening tool is effective and suitable for human immunodeficiency virus (HIV)-seropositive women. The aim of this review was to assess, synthesise and document published evidence relating to the available cervical cancer screening modalities for HIV-seropositive women in developing countries. This paper did not review the issue of human papillomavirus (HPV) prophylactic vaccine on HIV-seropositive women.

Methods: Five electronic databases were systematically searched from inception to January 2018 for relevant published original research examining cervical cancer prevention modalities for HPV infection, abnormal cytology and direct visualisation of the cervix amongst HIV-seropositive women in developing countries. Extra studies were identified through reference list and citation tracking.

Results: Due to methodological and clinical heterogeneity, a narrative synthesis was presented. Of the 2559 articles, 149 underwent full-text screening and 25 were included in the review. Included studies were of moderate quality, and no exclusions were made based on quality or bias. There is no standard cervical cancer screening test or programme for HIV-seropositive women and countries screening according to available resources and expertise. The screening methods used for HIV-seropositive women are the same for HIV-negative women, with varying clinical performance and accuracy. The main cervical cancer screening methods described for HIV-seropositive women are HPV deoxyribonucleic acid/messenger RNA (DNA/mRNA) testing ($n = 16$, 64.0%), visual inspection with acetic acid (VIA) ($n = 13$, 52.0%) and Pap smear ($n = 11$, 44.0%). HPV testing has a better accuracy/efficiency than other methods with a sensitivity of 80.0–97.0% and specificity of 51.0–78.0%. Sequential screening using VIA or visual inspection with Lugol's iodine (VILI) and HPV testing has shown better clinical performance in screening HIV-seropositive women.

Conclusion: Although cervical cancer screening exists in almost all developing countries, what is missing is both opportunistic and systematic organised population-based screenings. Cervical cancer screening programmes need to be integrated into already existing HIV services to enable early detection and treatment. There is a need to offer opportunistic and coordinated screening programmes that are provider-initiated to promote early identification of cervical precancerous lesions.

Systematic review registration: PROSPERO CRD42018095702

Keywords: Cervical cancer, Prevention, HPV, HIV, Developing countries

* Correspondence: witnessmapanga@yahoo.co.uk
[1]School of Health Systems and Public Health, Epidemiology & Biostatistics, University of Pretoria, 5-10 HW. Snyman Building, Pretoria, South Africa
[5]Harare, Zimbabwe
Full list of author information is available at the end of the article

Mapanga et al. Systematic Reviews (2017) 6:91
DOI 10.1186/s13643-017-0484-9

Systematic Reviews

PROTOCOL Open Access

Prevention of cervical cancer in HIV-seropositive women from developing countries: a systematic review protocol

Witness Mapanga[1,6*], Ahmed Elhakeem[2], Shingairai A. Feresu[1], Fresier Maseko[3] and Tsungai Chipato[4,5]

Abstract

Background: Over 85% of cervical cancer cases and deaths occur in developing countries. HIV-seropositive women are more likely to develop precancerous lesions that lead to cervical cancer than HIV-negative women. However, the literature on cervical cancer prevention in seropositive women in developing countries has not been reviewed. The aim of this study is to systematically review cervical cancer prevention modalities available for HIV-seropositive women in developing countries.

Methods/design: This protocol was developed by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement, and the systematic review will be reported in accordance with the PRISMA guidelines. Embase, MEDLINE, PubMed, CINAHL and Cochrane Library will be searched from inception up to date of final search, and additional studies will be located through citation and reference list tracking. Eligible studies will be randomised controlled trials, prospective and retrospective cohort studies, case-control and cross-sectional studies carried out in developing countries. Studies will be included if they are published in English and examine cervical cancer prevention modalities in HIV-seropositive women. Results will be summarised in tables and, where appropriate, combined using meta-analysis.

Discussion: This review will address the gap in evidence by systematically reviewing the published literature on the different prevention modalities being used to prevent cervical cancer in HIV-seropositive women in developing countries. The findings may be used to inform evidence-based guidelines for prevention of cervical cancer in seropositive women as well as future research.

Systematic review registration: PROSPERO CRD42017054678.

Keywords: Developing countries, Cervical cancer, HIV, Prevention

Background

Cervical cancer morbidity and mortality constitutes a growing burden in developing countries like Zimbabwe, Kenya, India, Botswana and South Africa; concern has shifted to how much can be done to prevent this public health challenge in all women with a lifetime risk approaching 1 in 20 in some developing settings [1]. A systematic review on the cervical cancer screening and prevention indicated that about 88% of all cervical cancer worldwide occurs in developing countries where there is very limited allocated resources to prevent and treat cervical cancer [1]. Research has shown that one has to be infected with human papilloma virus (HPV) to develop cervical cancer, but HPV alone does not fully explain cervical cancer epidemiology hence a number of cofactors associated [2, 3].

With the adverse of HIV in most of these developing countries especially those in sub-Saharan Africa, the burden of cervical cancer is increasing. HIV, which is a risk factor for cervical cancer, lowers women's immune system, making them more susceptible to HPV infection [4–7]. Globally, 1 to 2% of HIV-negative women develop cervical intraepithelial neoplasia (CIN) stages 2 and 3 annually whilst HIV-positive women are at 10% more

* Correspondence: witnessmapanga@yahoo.co.uk
[1]School of Health Systems and Public Health, Epidemiology and Biostatistics, University of Pretoria, S-10 H.W. Snyman Building, Pretoria, South Africa
[6]47 Newstead Road, Old Marlborough, Harare, Zimbabwe
Full list of author information is available at the end of the article

Mapanga et al. Systematic Reviews (2018) 7:22
DOI 10.1186/s13643-018-0686-9

Systematic Reviews

PROTOCOL Open Access

Treatment of cervical cancer in HIV-seropositive women from developing countries: a protocol for a systematic review

Witness Mapanga[1,3*], Tsungai Chipato[2] and Shingairai A. Feresu[1]

Abstract

Background: Cervical cancer has become the most common cancer affecting women in Africa. Significantly, 85% of these annual deaths occur in the developing world, with the majority being middle-aged women. Research has shown that in sub-Saharan Africa, cervical cancer trends are on the rise in the past two decades because of HIV and this has resulted in an increase in cervical cancer cases among young women. However, little or no information exists that has shown that any of the available treatment methods are more effective than others when it comes to treating cervical cancer in HIV-seropositive women. The aim of this protocol is to offer a plan on how to systematically review cervical cancer treatment methods available for HIV-seropositive women in developing countries.

Methods/design: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement was used to develop the protocol for the systematic review which will be reported in accordance with the PRISMA guidelines. A number of databases, Embase, MEDLINE, PubMed, CINAHL and Cochrane Library, will be searched for relevant studies, and citation and reference list tracking will be used to search for additional studies. Prospective and retrospective cohort studies, case-control, randomised controlled trials and cross-sectional studies that were carried out in and for the developing world will be eligible for inclusion. Peer-reviewed studies and grey literature examining cervical cancer treatment modalities in HIV-seropositive women will be included. Descriptive statistics and tables will be used to summarise results, and meta-analysis will be used where appropriate.

Discussion: The review findings will provide the current picture of the existing treatment methods being used to treat cervical cancer in HIV-seropositive women in developing countries. The findings might be used for the establishment of evidence-based guidelines for treatment of cervical cancer in seropositive women as well as prompt policy-makers and governments to decide and support future research in a way to find a lasting solution.

Systematic review registration: PROSPERO CRD42017054676
https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=54676

Keywords: Developing countries, Cervical cancer, HIV, Treatment

* Correspondence: witnessmapanga@yahoo.co.uk
[1]School of Health Systems and Public Health, Epidemiology & Biostatistics, University of Pretoria, 5-10 HW Snyman Building, Pretoria, South Africa
[3]47 Newstead Road, Harare, Marlborough, Zimbabwe
Full list of author information is available at the end of the article

Journal of Community and Public Health Nursing

Mapanga et al., J Comm Pub Health Nurs 2017, 3:3
DOI: 10.4172/2471-9846.1000180

Commentary OMICS International

A Commentary on a Systematic Review Protocol and Commentary on Cervical Cancer Prevention in HIV-Seropositive Women from Developing Countries

Witness Mapanga[1,2*], Shingairai A Feresu[1,2] and Tsungai Chipato[3]

[1]*Department of Epidemiology and Biostatistics, School of Health Systems and Public Health, University of Pretoria, 5-10 H.W. Snyman Building, Pretoria, South Africa*

[2]*College of Health Sciences, University of Zimbabwe-University of California, San Francisco, USA*

[3]*Collaborative Research Programme, University of Zimbabwe, Avondale, Harare, Zimbabwe*

***Corresponding author:** Witness Mapanga, MPH, Ph.D., Department of Epidemiology and Biostatistics, School of Health Systems and Public Health, University of Pretoria, 5-10 H.W. Snyman Building, Pretoria, South Africa, Tel: +263775142253; E-mail: witnessmapanga@yahoo.co.uk

Received date: May 30, 2017; **Accepted date:** June 08, 2017; **Published date:** June 15, 2017

Systematic Review Protocol Summary

The review protocol has indicated how gaps in evidence may be addressed by through reviewing of published literature on cervical cancer prevention strategies that are being used in developing countries for HIV positive women. The evidence that is going to be shown in this systematic review may be used to update and plug in the gaps in the cervical cancer screening and prevention among HIV positive women. The review guided by this protocol may also inform future research as well as form the basis of evidence-based strategies, policies and interventions for cervical cancer prevention. The systematic review is currently being conducted thus limitations and strengths of this protocol have not been considered. The validity of the findings from the informed review is going to be analysed and reported in relation of reviews and researches that are relevant.

Authors' Objectives

To document how to carry out a systematic review looking at the current strategies and interventions which are being used in the developing countries to screen and prevent cervical cancer in women who are HIV-seropositive. The systematic review will try to answer the following questions:

- Are there differences among countries on cervical cancer screening and prevention modalities which are being used for HIV-seropositive women?
- Have these cervical cancer screening and prevention methods improved over time?
- Are these cervical cancer screening and prevention modalities effective in preventing cervical cancer in HIV-seropositive women?

Searching

The following electronic databases, Cochrane, CINAHL, PubMed, Embase and MEDLINE, are being searched for studies that reported in English language. Additional studies for the systematic review are being searched via citation and reference tracking.

Study selection

The following study types; randomized controlled trials, prospective and retrospective cohorts, cross-sectional and case-control studies that enrolled women and looking at cervical cancer screening and prevention modalities and HIV, are eligible for inclusion. Included studies are required to be peer-reviewed, done in or for developing countries as defined by the United Nations and measures the effect or impact of the cervical cancer screening and prevention modality on HIV-seropositive women.

Studies' follow-up rates are being used as a measure of the quality of the studies' findings; therefore, no studies are being excluded as a result of length of follow-up. A study with a follow-up rate that is less than 60% is being considered of limited validity especially when loss to follow-up is associated with both screening and prevention modality and its cervical cancer prevention impact.

The studies' exclusion criteria includes reviews, studies which have unrepresentative samples and studies which were done looking at cervical cancer in general. Unrepresentative samples within studies are being determined and identified by performing non-parametric tests which are based on the demographical and geographical representation of the used sample against the population from which the sample was selected [1].

Results from the different database searches are being merged by two independent researchers who are also screening the abstracts. The abstract are being double-screened and the reasons for exclusions of some studies are documented to facilitate the process of discussion around disagreements arising through the screening process.

Assessment of study quality

Ascertainment of the quality of included studies is being done using the Newcastle-Ottawa Quality Assessment Scale which was modified for this review. Quality of the studies is being based on their designs, focus of the study, findings, length of follow-up and representativeness of participants. Within the specific study designs, further quality aspects looking at randomization of participants, blinded outcome, power calculation and whether the outcome measure was predefined. Quality examination of the studies is being done by two independent reviewers who are scoring the studies from zero (low quality) to five (high quality).

Data extraction

Data to facilitate meta-analysis is being extracted by two independent working reviewers.

Methods of Synthesis

Narrative synthesis is going to be used to summarize the characteristics of included studies through the use of tables. Meta-analysis is going to be used where there is sufficient consistency is the methods and results of the included studies. Findings from the