UNIVERSITY OF CAPE COAST

HUMAN PAPILLOMAVIRUS TESTING FOR CERVICAL CANCER AMONG WOMEN LIVING WITH HIV AT THE CAPE COAST TEACHING HOSPITAL, GHANA

SALIA EMMANUEL

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BY

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Thesis submitted to the Department of Microbiology and Immunology of the College of Health and Allied Sciences, School of Medical Sciences, University of Cape Coast, in partial fulfilment of the requirements for the award of Master of Philosophy degree in Infection and Immunity

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DECLARATION

Candidate's Declaration

I hereby declare that this thesis is the result of my original research and that no part of it has been presented for another degree at this University or elsewhere.

Candidate's Signature ……. Date ……

Name: ……

Supervisors' Declaration

We hereby declare that the preparation and presentation of the thesis were supervised following the guidelines on supervision of thesis laid down by the University of Cape Coast.

Supervisor's Signature ……... Date ……

Name: ……

Co-Supervisor's Signature ……. Date ……

Name: ……

ABSTRACT

Cervical cancer (CC) is a global health problem, with about 500,000 incident cases and 280,000 mortalities yearly. In Ghana, CC is the second commonest cancer associated with mortality and morbidity. Women living with HIV (WLHIV) are at a higher risk of developing pre-cervical cancer lesions. The world health organization (WHO) recommends Human Papillomavirus (HPV) DNA test for CC screening among women. This study determined the role of HPV DNA testing for CC screening among WLHIV at the Cape Coast Teaching Hospital (CCTH). A facility-based cross-sectional study was conducted among 330 WLHIV at the gynecology and antiretroviral therapy clinics at CCTH. Cervical samples were self-collected and screened using the Atilla Biosystems Ampfire systems (Atila Biosystems, Mountain View, CA, USA). Socio-demographic, behavioral, and clinical characteristics of participants was obtained using a standardized questionnaire. Stata v.16 was used to analyze the data. The mean age was 47.2 (SD ±10.7). The prevalence of hr-HPV and multiple hr-HPV were 42.7% (95% CI: 37.4-0.48.1) and 60.3% respectively. HPV59 (50.4%), HPV18 (30.5%), HPV35 (26.2%), were the most prevalent genotypes. Educational level (AOR=7.55, 95% CI: 1.34-42.43, p=0.022) was associated with CC knowledge. HIV viral load ≥1000 copies/ml (AOR=5.58, 95% CI: 2.89-10.78, p<0.001) was associated with co-infection. The knowledge level of WLHIV on CC is low and the prevalence of hr-HPV in this study is high. There is the need for intensified surveillance and a comprehensive CC prevention programme for WLHIV in Ghana.

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DEDICATION

To my parents, Very Rev. James Musah Salia and Mrs. Grace Fatima Salia,

and my sister, Elizabeth Zenabu Salia

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LIST OF ABBREVIATIONS

AIDS	Acquired Immuno-Deficiency Syndrome
AIM 2	Absent in Melanoma 2
AOR	Adjusted Odds Ratio
ART	Anti-Retroviral Therapy
ASCUS	Atypical Squamous Cells of Undetermined Significance
ASIR	Age Standardized Incidence Rate
CCTH	Cape Coast Teaching Hospital
CD4+	Cluster of Differentiation 4
CD 8	Cluster of Differentiation 8
CA-125	Cancer Antigen 125
CC	Cervical Cancer
CI	Confidence Interval
CIN	Cervical Intraepithelial Neoplasia
DNA	Deoxyribonucleic Acid
EGFR	Epidermal Growth Factor Receptor
FIGO	International Federation of Gynecologists and Obstetrics
HAART	Highly Active Antiretroviral Therapy
HC2	Hybrid Capture 2
HDI	Human Development Index
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HR-HPV	High-Risk Human Papilloma Virus
H-SIL	High-Grade Squamous Intraepithelial Lesions
IARC	International Agency for Research on Cancer
ICC	Invasive Cervical Cancer
IF 1	Type 1 Interferon
IGF-II	Insulin-like Growth Factor II
KC	Keratinized Cells
KP	Key Populations
LB	Lysis Buffer

LCR	Long Control Region
LSIL	Low-Grade Squamous Intraepithelial Lesions
LMIC	Low-to Middle-Income Countries
MAPK	Mitogen-Activated Protein Kinase
MSM	Men Sleeping with Men
NF-kB	Nuclear Kappa Factor B
NHANES	National Health and Nutrition Examination Survey
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
ORF	Open Reading Frames
PCR	Polymerase Chain Reaction
PMTCT	Prevention of Mother to Child Transmission
PLHIV	People Living With HIV
RIG	Retinoic Acid Inducible Gene 1
SAE	Significant Adverse Effect
SC	Self-Collection
SIL	Squamous Intraepithelial Lesions
SOP	Standard Operating Procedure
SSA	Sub Saharan Africa
STAT 3	Signal Transducer and Activator of Transcription 3
STI	Sexually Transmitted Infection
TGN	Trans-Golgi Network
TLRs	Toll-Like Receptors
URR	Upstream Regulatory Region
VEGF	Vascular Endothelial Growth Factor
VIA	Visual Inspection with Acetic acid
VILI	Visual Inspection with Lugol's iodine
VLP	Virus-Like Particle
WHO	World Health Organization
WLHIV	Women Living with HIV

CHAPTER ONE

INTRODUCTION

This section of the study provides the essential context and background for the issues explored in the research, while also introducing the key concepts and theories that underpin the study. The chapter commences with a broader discussion on cervical cancer (CC) within the global health discourse, progressing to the epidemiology of human papillomavirus (HPV) and subsequently narrowing the discussion to the association between HPV and HIV infections in women living with HIV (WLHIV). Moreover, the chapter introduces the HPV genotypes that are in circulation globally and among WLHIV, as well as the prevention strategies available for women who are vulnerable to HPV infection. These discourses serve as the foundation for formulating the problem statement and study objectives. Finally, the chapter concludes with a succinct articulation of the study's significance, delimitations, and organization. In essence, this section forms the bedrock for the study by providing the reader with an understanding of the context, concepts, and theories that will be explored in the subsequent sections.

Background to the Study

CC is a global health problem, with about 500,000 incident cases and 280,000 mortalities yearly (Arbyn et al., 2020). HPV is known to be the ideal cause of cervical cancer among women globally (Arbyn et al., 2020) and the discovery of persistent infection with carcinogenic HPV leads to the creation of novel CC preventive strategies (IARC, 2007). In low-middle income countries (LMIC), the incidence of cervical cancer is on the rise with annual 85% new cases and 87% mortality recorded (Krings; et al., 2019). Factors

such as underdeveloped health facilities, inadequate technological testing and funding (Dunyo et al., 2018), poor awareness programmes, and the unavailability of the right human resource for testing, management, and treatment of cervical cancer (Denny et al., 2016) hamper testing and diagnosis. It is predicted that by 2030, the incidence of cervical cancer will rise by 90% globally (De Vuyst et al., 2013). In Africa, the differences in cervical cancer incidence have been linked to a variety of variables, including variations in the underlying frequency of high-risk HPV infection in women and discrepancies in the availability of efficient cervical cancer diagnosis, treatment, and prevention centers (Awolude et al., 2013). In West Africa, HPV is found in 20% of women who have no aberrant cytology, compared to a global average of 12% (De Vuyst et al., 2013; Forman et al., 2012).

Although HPV vaccinations are obtainable and offer good protection, the accessibility in countries like Ghana is very much dependent on Global Alliance for Vaccines and Immunization activities (Krings; et al., 2019). Additionally, current vaccines do not include all high-risk HPV genotypes, necessitating the use of easy, economical, and acceptable secondary prophylaxis. Although the benefits of HPV testing for CC screening are well established, it remains infrequent (Tsu et al., 2018). CC is the second commonest cancer and also, the second major cause of cervical cancer-related mortality and morbidity in Ghana constituting 1699 gynecological cancer deaths annually (Bruni. et al., 2019), and Sub-Saharan Africa (SSA), recording a projection of 3052 new cases and 1556 deaths per year (de Sanjosé et al., 2015; Ferlay et al., 2019). Similarly, the primary cause of cancer-associated deaths in Botswana is CC with about two-thirds of the cases

occurring among women with underlying conditions (Mapes et al., 2016). Data on HPV occurrence and genotype distribution among women in Ghana point to HPV involvement in causing cervical cancer (Donkoh. et al., 2022).

Over 140 HPV genotypes have been discovered globally, out of which 40 genotypes are capable of infecting the genital mucosa and have been categorized as high-risk HPV(hr-HPV), low-risk HPV (lr-HPV), and intermediate HPV infection based on their oncogenic potentials (De Sanjose et al., 2010). hr-HPV infection is attributed to cervical cancers globally (De Martel et al., 2012; Wheeler, 2008). Among hr-HPV, only HPV16 and HPV18 account for 70% of CC cases globally (de Sanjosé et al., 2012; Lu et al., 2015). HPV genotypes 16, 18, 31, and 33 are ubiquitous globally (De Sanjose et al., 2010) with HPV16, 18, 33, and 35 being common in SSA, indicating regional variation for HPV genotype distribution in cervical cancer infection globally (Denny et al., 2014). Considering the various risks HPV vaccination could protect against infection and cancer progression, it is therefore imperative to investigate HPV genotype distribution and prevalence in all regions of the globe (Krings; et al., 2019) through appropriate HPV testing.

In developed countries where diagnosis and treatment schedules are developed, cervical cancers are principally avoidable and curable (Engholm et al., 2012; Peirson et al., 2013). It is most appropriate when cervical cancer screening programs are based on local research, customized to the populace and resource infrastructure (Ginsburg et al., 2017). HPV testing is mostly employed in developed countries in diagnosing cervical intraepithelial neoplasia (CIN) and squamous intraepithelial lesions (SIL) due to its high sensitivity (Cuzick et al., 2012; Roberts et al., 2011). High-profile molecular

diagnostics such as polymerase chain reaction (PCR) for HPV genotyping which are mostly employed in discovering and characterizing HPV are unlikely accessible in most LMICs such as Ghana (Obiri-Yeboah et al., 2017).

For screening women in the general population and WLHIV, the WHO advises utilizing HPV testing as the primary screening test instead of visual inspection with acetic acid (VIA) or cytology (WHO, 2021b). The identification of HPV infections and associated clinical signs is challenging in Ghana (Ebu et al., 2015). However, self-collection of samples and the accessibility of simple molecular diagnostics, such as the care HPV test, which has demonstrated good sensitivity and specificity, make it a relevant strategy for community-level screening (Obiri-Yeboah; et al., 2017). Also, the dependence on clinicians in taking CC samples for testing affects tolerability and coverage of testing (Ebu et al., 2015). Hence, a recent study suggests that self-collection (SC) of cervical samples improves compliance for sampling (Obiri-Yeboah; et al., 2017). Many women may not have time to visit clinics for sample taking and the passage of a speculum into the vagina during sample collection may be unconformable to most and hence deterring them from participation to screening discomforting to most women hence deterring them from participating (Obiri-Yeboah et al., 2017). In Ghana, other than a woman's spouse, it is culturally unacceptable for most people that another person sees the genital areas (William et al., 2013) and all these constitute barriers to CC screening in Ghana.

The human immunodeficiency virus (HIV) infects an estimated 36.9 million persons worldwide (UNAIDS, 2018). Around 75% of HIV-positive women reside in Sub-Saharan Africa (SSA) (UNAIDS, 2018). Remarkably,

patients with HIV have an increased life expectancy rate due to excellent HIV treatment and control initiatives. However, this longer life expectancy has resulted in a higher chance of developing noncontagious illnesses, such as cancer (Kharsany and Karim, 2016; White et al., 2014).

Globally, there are more WLHIV than males. In Ghana, about 60% of people living with HIV are women (Farouq, 2016; UNAIDS, 2018). WLHIV have HPV prevalence higher than the global value between 15% to 45% (De Sanjosé et al., 2007). HIV-HPV coinfection has serious ramifications for both HIV patients and health professionals. Infection with HIV increases the chances for HPV infections and cervical lesion development (Jalil et al., 2013; Patel et al., 2013). However, it has been established that an improved $CD^{+}4$ levels in persons with HIV helps in the clearance of HPV (Konopnicki et al., 2013b) and also, the usage of antiretroviral therapy (Forman et al.) among HIV-positive women minimizes HPV-related clinical conditions (Blitz et al., 2013).

Prevention methods for HPV and HIV are centered on community-based publicity on safe sex practices and abstinence. The use of bivalent, quadrivalent and nano-valent vaccines for HPV have helped in preventing HPV16, 18, 6, 11, 31, 33, 45, 52, and 58 types (Alder, 2018). In 2013, an experimental HPV vaccination exercise was carried out among girls between 9 to 13 years using the quadrivalent vaccine (Wigle et al., 2013).

The chances of developing cervical pre-cancerous lesions are higher among WLHIV than in women negative for HIV (Constantine et al., 2020). The best screening and prevention approaches for WLHIV of various ages are limited. This is based on accumulated study findings that suggest that HIV

coinfection modulates HPV and cervical cancer epidemiology and the influence of antiretroviral therapy (Forman et al.) on this epidemiology (de Vries and Steenbergen, 2018; Kelly et al., 2018).

In Africa, hr-HPV 16, 18, and 45 are greatly linked with cervical cancer (Daneshvar et al., 2017; Vernet-Tomas et al., 2015). Coinfection of hr-HPV types and other forms of HPV infection among WLHIV advances the chances of developing cervical cancer (Denny, 2012; Lowy, 2016). More so, the reduced number and function of a cluster of differentiation 4 (CD^+4) T-cells due to HIV infection increases HPV infection and minimizes the chances of HPV clearance by the immune system (Lowy, 2016). Though several researchers have studied hr-HPV genotypes determining the is important in establishing the HPV burden in such countries endemic to HIV, ascertaining the distribution of hr-HPV among WLHIV using HPV DNA testing is prudent in determining the HPV burden in countries endemic to HIV (Clifford et al., 2016; Lowy, 2016). The Access to and availability of HPV vaccines have been the challenge of LMICs (Ayissi et al., 2012; Campos et al., 2012).

Problem Statement

The fourth regular neoplasm among women globally is cervical cancer (Bray et al., 2018; WHO, 2020a). Although most cases of cervical cancer are recorded in Africa, SSA contributes 1% of global scientific data on cervical cancer (Aarnio et al., 2020). In LMICs, women make up 52% of all PLHIV, according to the Joint United Nations Programme on HIV/AIDS (UNAIDS) report, but SSA has the highest percentage (57%) of WLHIV (WHO, 2021b). Due to HIV mediated immunosuppression, WLHIV have an increased risk of developing CC (Dugue et al., 2013). In Ghana, CC is the leading cause of

death among women, particularly those between the ages of 15 and 44 (Mensah and Mensah, 2020). However, about 90% of WLHIV have never been screened for CC due to many factors including the unlikelihood that women with HIV will visit gynecology clinics compared with HIV clinics (Peprah et al., 2018). In Ghana, HPV diagnosis is met with several challenges. Pap smear is the commonest diagnostic test in Ghana but only accessible in metropolitan districts. Most women only seek pap smear test when they have gynecological symptoms. Also, Ghana's socio-cultural beliefs make it unacceptable for the genitals of a female to be seen or touched by another person not a relative or husband, sampling using a speculum through the vagina for screening by a doctor (male or female) remains a barrier (Obiri-Yeboah et al., 2017)

In 2020, the WHO initiated the global plan to hasten the eradication of cervical cancer through 90% HPV vaccine coverage and 70% screening success. The use of HPV DNA testing in both the general population and among WLHIV as the primary diagnostic tool has been strongly proposed (WHO, 2021b). However, with the scarcity of epidemiological data on HPV among WLHIV in Ghana, it is imperative to determine the hr-HPV genotype distribution among this group of women

Aim

This project goal is to determine the HPV prevalence and genotype distribution among WLHIV at the Cape Coast Teaching Hospital.

Specific objectives

To achieve this aim among WLHIV, the following specific objectives have been proposed to:

1. Determine the knowledge of WLHIV on cervical cancer and HPV
2. Determine the prevalence of hr-HPV among WLHIV.
3. Establish the specific HPV genotypes circulating among HIV/HPV co-infected women at the CCTH.
4. Establish the risk factors associated with hr-HPV infection among WLHIV at the CCTH.

Justification

The influence of HPV-HIV coinfection on infected persons may be enormous due to the potential synergistic effect. High HPV levels may affect HIV viral loads in individuals co-infected with both viruses (Ruffieux et al.)

It was projected that 55% of PLHIV globally were women and girls (UAIDS, 2021). There is an improvement in the life expectancy of WLHIV due to the availability of ART (Pellowski et al., 2019), signifying that several women with HIV may be harboring HPV infection resulting in high prevalence and incidence with the associated risk of developing cervical lesions and cancer. It is therefore important to determine the prevalence of hr-HPV infection among WLHIV in Ghana. Knowing the various HPV genotypes prevalent in Ghana will also help provide evidence that will inform national vaccination plans.

Delimitation

The study population includes women with HIV AIDS who visits the ART unit of the Cape Coast Teaching Hospital. HPV samples taken were either dry swap samples or cervical cell suspension. The molecular diagnostic assay chosen for HPV testing was based on previous literature and the types of HPV endemic in the region.

Limitation

The insurgence of COVID-19 slowed down the study participants' recruitment process for the study. Similarly, due to the CVID-19 pandemic, borders were closed and shipping of molecular items was delayed. The cost of molecular test kits is extremely expensive and that has hampered slightly procurement of study items for the early commencing of the study.

Organization of Study

This research is divided into five sections. The initial section covers the context, problem statement, importance, objectives, limitations, scope, and structure of the study. The second section examines pertinent literature on HPV biology, epidemiology, and pathogenesis, as well as the interplay between HPV, HPV, and HIV in cervical cancer development, as well as strategies for preventing and treating HPV and cervical cancer in LMIC. The third section outlines the techniques, materials, study sites, inclusion and exclusion criteria for research participants, ethical concerns, data collection, analysis, and management. The fourth chapter presents the research results and provides extensive analysis of the obtained outcomes in relation to the relevant literature. The fifth chapter presents conclusions drawn from the research findings, provides necessary recommendations, and proposes further advanced research.

CHAPTER TWO

LITERATURE REVIEW

Introduction

In this chapter, the study reviewed the natural history of HPV globally and in SSA, the epidemiology of HPV-HIV coinfection around the globe, SSA and in Ghana, and the rate of HPV-associated cervical cancer in SSA and Ghana. This chapter further evaluates the various categories of HPV that causes pre-cancer and cancer globally and the genotypes prevalent in SSA and Ghana. The various diagnostic methods available for detecting cervical lesions, precancers, or cancer, and possible preventive measures available to curb transmission were also addressed.

Databases that were used in the conduction of the literature review included: PLOS, PubMed, Medline, Google Scholar, Web of Science, and WHO. Mesh headings such as "Detection of HPV DNA among cervical samples", "Epidemiology of HPV-HIV coinfection", "Prevalence of HPV in HIV population", "Molecular characterization of HPV among WLHIV", and other relevant phrases were searched for in the databases.

HPV classification and genome

HPV belongs to the *Papillomaviridae* family and is divided into 53 genera (Institutet, 2021). Five out of the fifty-three genera cause diseases in humans. HPV genera are dependent on sequence similarities with the L1 opening reading frame (ORF). HPV which is 60% less similar to the major L1 protein is categorized as a distinct genre. HPVs that are 60-70% similar to the L1 protein within a genus are classified as species. 71%-89% of similarities with L1 within a species are considered a type. More so, 90-98% and above

98% similarity in nucleotide sequences of HPV are known as subtypes and variants respectively. (International Human Papillomavirus (HPV) Reference Center, 2021). By December 2020, about 222 HPV types are known which are categorized into five genera that are associated with human diseases. Fifty-four HPV types form the genera Betapapillomaviruses, and a single HPV form the Alphapapillomaviruses, Gamapapillomaviruses, Mupapapillomaviruses, and Nupapillomaviruses respectively. The affinity of each genus, as determined by the interaction of the viral L1 capsid protein with cell surface cells during viral entry differs (Doorbar et al., 2015). Except for the Alphapapillomaviruses group that has a tropism for mucous membranes causing cancer, the rest have an affinity for cutaneous membranes causing warts in the hands and feet. α-HPV is classified into hr-HPV and lr-HPV depending on their capability to alter cells leading to cancer. Infections by lr-HPV 6 and 11 lead to anogenital warts formations and are said to be noncarcinogenic. On the other hand, infection by hr-HPV 16,18, etc leads to cancer development in the cervix, anal, penile, vulvar, head, and neck (WHO, 2019a). About 5% of cancers globally is attributed to hr-HPV16,18,31,33,35, 39,45,52,56,58,59,66 and 68 infections.

The HPV genome is non-enveloped with a double-stranded genome which is closed circular (Fig. 1), 8kbs in size and that has a high affinity for squamous epithelium. The HPV genome is made up of the early region which has six regulatory proteins, the late region which has two structural proteins, and the long control region (LCR) or non-coding upstream region (Tsu et al.). The early region has two large (E1 and E2) and numerous minor (E6-E7) ORF. The E1 protein enhances helicase and ATPase activity by binding to the

viral origin of replication. It also forms a complex with E2 and facilitates its attachment to the source of replication. The E2 protein is fully engaged in the viral DNA replication by recruiting E1 to the viral genome origin, modulation of transcription of the virus, and separating viral genomes (Kardani and Bolhassani, 2018). The E4 suppresses viral DNA replication via the blockage of the G2-to-M transition and alters the function of cellular mitochondria. E5 in the presence of epidermal growth factor (EGF) stimulated the proliferation and immortalization of human keratinocytes (Kardani and Bolhassani, 2018). The E5 also reduces the acidity of endosomes; and elevates ligand-depended signaling. E6 proteins inhibit HPV E7-induced apoptosis and facilitate viral replication (Guion et al., 2019). E7 protein diversifies the presence and location of cellular proteins as well as increases their presence in the cytoplasm. It also has an affinity for retinoblastoma and reduces apoptosis via binding to glutathione S-transferase P1 and prevents the phosphorylation of JNK (Guion et al., 2019). The HPV genome is protected by a capsid made up of seven two (72) capsomeres each made up of 55KDa monomers that bond to form a pentamer which corresponds to the protein L1 (Vashisht et al., 2019).

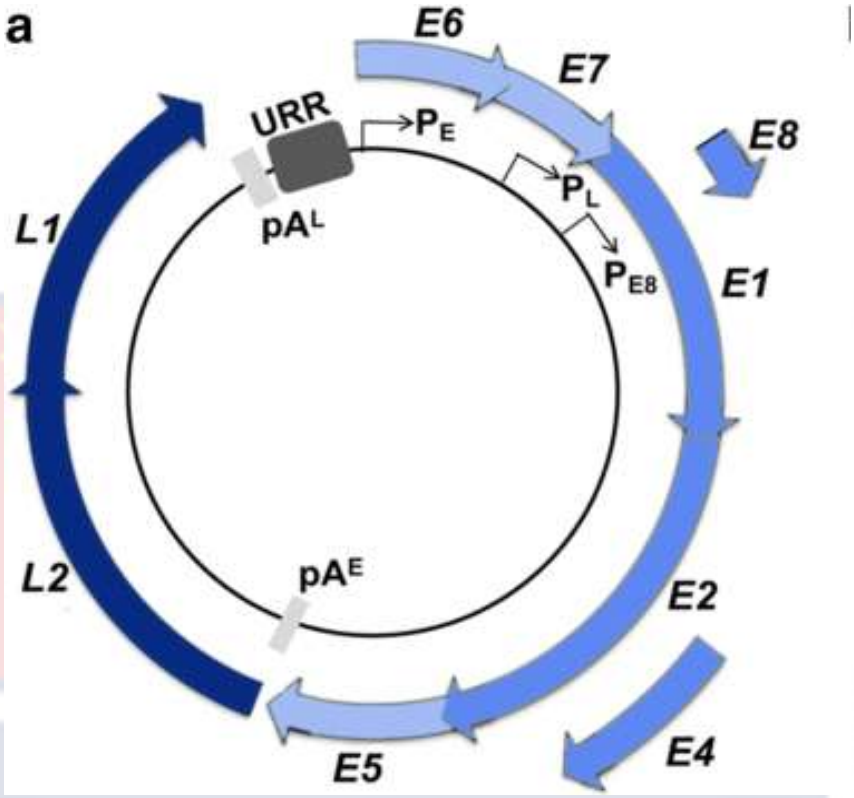

Figure 1: Human Papillomavirus genome *Adopted from* (Burley et al., 2020).

The lifecycle of HPV

The HPV virus does not undergo self-replication due to its inability to encode enzymes or polymerase that will enable the process. It however depends on actively dividing basal cells of the infected host such as the mucosal squamous or cutaneous epithelia to undergo genome replication and establish an infection (Rengifo-Rodríguez et al., 2020). In the cervix, HPV targets the junctions (specialized stem cells) where there is no requirement to cause a tear to initiate infection. This target region is the point where there is a transition of the epithelium from the "columnar epithelial cells of the endocervix to the stratified squamous epithelium of the ectocervix" (Doorbar and Griffin, 2019). Host cells are invaded by HPV through endocytosis (Aksoy et al., 2017; Raff et al., 2013) and they migrate to low PH environments, such as the lysosomes and endosomes, where the genome

capsid is uncoated (Aksoy et al., 2017). One of the late proteins of HPV, L2, remains connected to the viral DNA and enhances its transfer to the host nucleus through the trans-Golgi network (TGN) (McBride, 2021). The HPV remains in the TGN throughout mitosis enabling it to escape the innate immune responses from the host (Cosper et al., 2021).

HPV lifecycle can be classified into three phases: the establishment phase, the maintenance phase, and the productive/vegetative phase (Syrjänen, 2018). The establishment phase comprises viral protein transcription and then viral DNA amplification. Amplification of the HPV genome is initiated by the viral proteins E1 and E2 (Graham, 2017; McBride, 2021). The E2 binds to the "origin of replication (Tsu et al.) on LCR" and recruits a helicase, an encoded enzyme of HPV, and E1 to the site of amplification forming a specific sequence complex. The E2 breaks away from the complex formed leaving E1 in the complex which then unwinds the viral DNA allowing host replication machinery to make copies of the viral genome (Piirsoo et al., 2020).

In the maintenance phase, during mitosis, the viral genome is divided into daughter cells (Culleton et al., 2017) by the fastening of the genome to host chromosomes by E2. Infection persists at this phase for a long time in the basal epithelial cells permitting the formation of premalignant precursor lesions that can progress to invasive cancer in a few cases or revert (Kehinde, 2020). Host immune responses mostly mediate the clearance of infection resulting in about 10% of cases progressing to cancer states (Kehinde, 2020).

After the maintenance phase is the vegetative or replication phase which happens in differentiating epithelial cells (Van Doorslaer et al., 2018) which then differentiates and migrates to the surface of the epithelium. At a

point in the replication process where differentiating cells seize to differentiate or become mitotically inactive and are unable to help in the viral DNA replication, the host cell DNA copying mechanism is stimulated by the viral proteins E6 and E7 permitting the continuation of the "viral DNA replication" (Warburton et al., 2021). The L1 and L2 proteins become expressed resulting in packaging, maturation, and release in a nonlytic mode from the outmost epithelial cell layers (Cosper et al., 2021).

HPV Pathogenesis and Cervical Carcinogenesis

The area of the body most susceptible to infection is the cervix, which is situated between the vagina and the uterus. The "stratified non-keratinizing squamous epithelium" lines the vaginal cavity. The "squamocolumnar" junction is particularly sensitive to high-risk HPV "transformation" (Doorbar and Griffin, 2019; Regauer and Reich, 2021). CC can manifest itself in two ways in the transition zone. The skin and mucosa are the most prevalent sites of infection.

Young women and adolescents who are sexually active are most commonly infected with HPV through sex, where the HPV virion causes infection in the basal epithelium through epithelial injuries or abrasions (Renjie et al., 2020), resulting in cervical dysplasia or CIN, which then progresses to hr-HPV infection, resulting in CC. The development of CC takes a while and can be divided into several stages (Jalil and Karevskiy, 2020). HPV infection could be diagnosed in clinical settings in the first stage, but the majority are diagnosed after 1to2 years without treatment (Cohen et al., 2019; Marth et al., 2017). The early genes, E1, E2, E4, E5, E6, and E7, are expressed after infection. After replication of the viral genome, the late genes, "L1 and

L2," and E4 are expressed, with production of young viral particles in the higher epithelium layers (Doorbar, 2006; Kajitani and Schwartz, 2022). The new virion infects new cells and also start replicating. Some HPV infections can persist for more than a year without treatment, which raises the risk of developing "high-grade squamous intraepithelial lesions (CIN2/3)" or possibly *invasive cancer*. (Kang et al., 2021; Renjie et al., 2020). Cervical cancer is caused by a combination of factors, including disruption of cell cycle control mechanisms, buildup of genetic damage due to the viral oncoproteins, as well as immune evasion (Kang et al., 2021).

HPV viral infection and immune responses

The majority of spontaneous HPV infections are limited to the mucosa's intraepithelial layer and do not progress to malignancy (Cubie, 2013; Wang et al., 2020). Nearly 90% of HPV-infected people have an innate and/or acquired immunity to the virus (Amador-Molina et al., 2013; Andersen et al., 2014). Humoral immune system mediated viral elimination develops after some months (Moscicki et al., 2012). A prolonged infection affects 10% of patients, and roughly 1% of all patients have an elevated risk of cancer (Moscicki et al., 2012). Chronic HPV infection is necessary in the progression of CC. In HPV tumorigenesis, the struggle between persistence and elimination is crucial. The host response detects infiltration of CD4+, CD8+ lymphocytes, and macrophages, as well as a rise in proinflammatory mediators and the generation of protective immunity, as the premalignant lesion progresses (De Vincenzo et al., 2013).

The entry of the HPV viral genome is detected by toll-like receptors (TLR) (Jee et al., 2021), interferon-inducible protein 16 (IFI16) (Jee et al.,

2021), cyclic guanosine monophosphate adenosine monophosphate synthase (cGAS) (Jee et al., 2021; Westrich et al., 2017) and absent in melanoma 2 (AIM2) (Jee et al., 2021). The attachment of the viral genome to host cell receptors initiates the generation of nuclear kappa factor B (NF-κB) and type 1 interferon (IF-1) via inducing "downstream signal transduction pathways" as well as Mitogen-Activated Protein Kinase (MAPK) through TIR or MyD88 (Jindal et al., 2021; Takeuchi and Akira, 2010). The combined efforts of these cellular mechanisms lead to the arrest and processing of the viral genome to the T cell which subsequently is cleared from the host system (Takeuchi and Akira, 2010). Except for keratinocytes (KCs), no other cell expresses the HPV genes. KCs quickly increase the expression/production of several pro-inflammatory mediators, including cytokines and chemokines, after recognizing the presence of HPV DNA via TLR9 or indirectly via RIG-I (Ablasser et al., 2009; Jee et al., 2021). Contrary to the host defense mechanisms, the HPV also deregulates the host defenses by obstructing DNA synthesis, cell cycle, and the STAT 3 and NF-κB pathways (Huang et al., 2019; Rezaul et al., 2011; Rezaul et al., 2013). Also, the HPV modifies Th1/Th2 responses in the early infection stages of the virus (Azar et al., 2004).

Global HPV infection

In individuals who have normal cytological results, prevalence is about 11.7% (Rettig et al., 2018; Scott-Wittenborn and Fakhry, 2021). The age distribution of HPV infection exhibits an exponential increase in early teens and twenties, followed by a gradual decline. Nevertheless, in some countries, a second peak occurs later in life (Franceschi et al., 2006). HPV16, 52, 31, and 53 are the most frequent "HPV strains infecting women with normal cytology"

worldwide; for CC, the primary strains are HPV16 and 18, which are responsible for nearly 55% and 14% of cervical malignancies, respectively (Bruni; et al., 2019b). With a cumulative of 690,00 cases of cancer globally in 2018, the complete "age-standardized incidence rate (Adjorlolo et al.)" for HPV-related cancers was 8.0 per 100,000 (de Martel et al., 2020). It is vital to consider that the majority of HPV-related malignancies affect women, thus sex-stratified figures are taken into account (Lopes-Ramos et al., 2020). As a result, the global ASIR rate for CC is 13.1 with a 6.9 per 100,000 fatality rate (Arbyn et al., 2020). It is the second commonest cancer in women below age of 50 and the fourth major cause of cancer death among women of all ages (Serrano et al., 2018).

According to multiple meta-analyses, about 4% to 20% of women in North America with normal cytology results are prevalent to HPV cervical cancer infection, with women in their 20s being the most prevalent (Serrano et al., 2018). The introduction of HPV vaccination program for young girls in the United States of America (USA) in 2007 has considerably reduced the HPV prevalence. The National Health and Nutrition Examination Survey (NHANES) (Rosenblum et al., 2021) data for 2018 revealed an 86% decline in HPV types for women aged 14-19, and a 71% decrease for *women* aged 20 to 24 through vaccination (McClung et al., 2019).

Like the USA, HPV prevalence in Western Europe is low. High HPV prevalence is recorded in Northern Europe (10%) and Eastern Europe (21.4%-29.1%) compared to Southern and Western Europe (9%) (Laia et al., 2010). However, some discrepancies in HPV prevalence in studies conducted in some

countries in Europe put the continent in heterogeneity in the evaluation of HPV prevalence (Scott-Wittenborn and Fakhry, 2021).

Sub-Saharan Africa (SSA) has one of the highest rates of HPV infection globally. Southern Africa has the lowest prevalence rate of 17% compared to West Africa (29%), North Africa (15-21%), and East Africa (33%); all of which peak above the worldwide average of 11% (Obeid et al., 2020). One significant challenging issue with the elevated frequency of HPV in SSA is the endemicity of HIV in the continent and the increased prevalence of HPV-HIV co-infection among WLHIV (Castle et al., 2020; Ndizeye et al., 2019). WLHIV are less likely to clear HPV and are highly vulnerable to developing cervical cancer (Stelzle et al., 2021).

In Asia and Oceania HPV prevalence among women without cytological lesions is 9.4% with Mongolia, Korea, and Oceania recording the highest (Bruni; et al., 2019a; De Sanjosé et al., 2007). In China, the prevalence in women without cervical lesions is 11%-15% (Kemin et al., 2019). The introduction of the HPV vaccination program saw a reduction in HPV prevalence from 21% to 9.25% in Australia (Brotherton et al., 2019; Tabrizi et al., 2014). India has a 5% of HPV in women with normal cytology. In an effort to minimize HPV prevalence in India through vaccination, maiden vaccine programs were deferred due to increasing deaths recorded (Brotherton et al., 2019; Sankaranarayanan et al., 2019).

In Latin and Central America, the HPV prevalence stands at 12.3% and 20.4% respectively (Bradford; et al., 2019; De Sanjosé et al., 2007). However, a combined prevalence *of* the two regions showed a 16.1% prevalence. HPV infection peaks up among youngsters between the ages of 14-19, decreases

among mid-age groups, and peaks again among women in their 50s (Sichero et al., 2020). However, the enrollment of HPV vaccination programs in most countries in southern and central America gives a positive indication of reducing HPV prevalence in the region (Niu et al., 2021).

Risk factors for HPV infection and persistence

- **Age:** In adolescence, the "glandular epithelium of the transformation zone" is susceptible, leading to higher prevalence of HPV among adolescent age range (Morhason-Bello et al., 2021; Watson-Jones et al., 2013). The strong metaplastic activity during puberty contributes to this susceptibility. However, after menopause, this metaplastic activity decreases, lowering the chance of HPV infections. Unless other factors improve persistence, HPV prevalence decreases beyond 30 years (Carozzi et al., 2014).
- **Age at first sexual contact:** A number of studies have reported an association with the age of first sexual contact (Asiaf et al., 2014; Kombe Kombe et al., 2021; Watson-Jones et al., 2013) The virus is acquired shortly after commencing sexual activity, and females may continue to acquire additional infections; therefore, determining the age at which girls in a certain demographic must be vaccinated is critical.
- **Immunosuppression:** HIV/AIDS is associated with low immunity (Ezechi; et al., 2014; Miguel Haddad Kury et al., 2021), and other factors that cause both primary and secondary cell-mediated immunodeficiency have been associated with an increased risk of

carcinogenesis in infected persons (Munoz et al., 2013; Shoja et al., 2019).

- **Multiple sexual partners:** Having more than one concurrent sexual partners or having a partner who has other sexual partners increases the chances or risk of HPV acquisition. Like other STI infections, co-infection with other STIs like herpes simplex virus type, Chlamydia, etc. increases the chances of HPV transmission and persistence (Shew et al., 2013).
- **Life-time sexual partners:** The more sexual partners one has the higher the chance of HPV infection**.** Women with five or fewer partners have lesser rates of infections than those with partners of more than five.
- **Condom Usage:** This provides some protection, but not complete protection because HPV can be transferred through portions of the vaginal area not covered by the condom, such as the scrotum (Dunne et al., 2003; Pierce Campbell et al., 2013).
- **Number of pregnancies:** It has been suggested that the more the number of pregnancies, the greater the risk (Pourmohsen et al., 2018; Ribeiro et al., 2015). This might be due to a greater rate of sexual activity among mothers with more children. As a result, there's a chance you'll be exposed to HPV at a greater rate.
- **Co-infection with other STIs:** Through immunological and other mechanisms, co-infection with other STIs enhances the likelihood of HPV infection and its persistence (Shew et al., 2013).

- **Use of hormonal contraceptives:** Progesterone is thought to have responsive components with a sequence comparable to HPV's upstream regulatory region. This might explain why women who have used hormonal contraceptive for long-term have greater risk of HPV persistence and CC (Gadducci et al., 2020; Kozasa et al., 2019; Momenimovahed and Salehiniya, 2017).
- **Smoking:** Cigarette smoking is thought to cause local immunosuppression as well as mutagenic elements, resulting in HPV infection persistence and enhanced malignant transformation (Zidi et al., 2020).

HPV Diagnosis

Several HPV molecular diagnostic techniques have been developed and evaluated in different populations. The well-known "Digene Hybrid Capture 2 (HC2) HPV DNA assay (Qiagen, France)" detects the 13 hr-HPV genotypes, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68, by hybridizing HPV DNA and chemiluminescence signal amplification (Salimović-Bešić et al., 2013; Vranic et al., 2020) which yielded a semi-quantitative outcome. This test has good performance and has been compared with other tests such as the "INNO-LiPA HPV genotyping assay" (Fujirebio, Ghent, Belgium), which is based on the PCR amplification of a fragment of the HPV L1 gene and detects 28 HPV types, including those detected by the "Digene HC2 HPV DNA assay", the "possible carcinogenic" HPV types 26, 53, 66. Ngou et al., have found that HC2 had lower analytical sensitivity but greater specificity than "INNO-LiPA" for detecting high-grade lesions while the two tests showed

equivalent clinical sensitivity to detect CIN2 and HSIL lesions (Ngou et al., 2013).

AnyplexTM II HPV28 (Seegene, Seoul, Korea) identify 28 different HPV strains, including high-risk strains "16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, 82" and low-risk strains "6, 11, 40, 42, 43, 44, 54, 61, 70". This technique was evaluated to the "Digene HC2 HPV DNA assay" (Qiagen, Gaithersburg, MD) and has been shown to be more sensitive in detecting the 13 hr-HPV types detectable by both assays, as well as having better agreement with "complete genotyping based on sequencing analysis" (Atchison et al., 2021; Kwon et al., 2014).

The *care*HPV assay (Qiagen, Gaithersburg, MD) is a semi-rapid test invented to identify DNA for 14 hr-HPV types (16, 18, 31, 33, 35, 39, 45, 52, 56, 58, 59, 66 and 68; HPV66 being the addition). This is based on a polymerase chain reaction and yields positive or negative results (AlBosale et al., 2021; Arbyn et al., 2014; Mitchell et al., 2014). It is reported to have been created for usage in resource-constrained environments such as SSA. In a study conducted in Ghana among type 1 seropositive HIV clients and seronegative HIV individuals, it was found that the *care*HIV assay was equally sensitive among the study groups but more specific among HIV seronegative participants (93.1%) compared to seropositive HIV-1 group (85%) (Obiri-Yeboah, 2017). Similarly, studies done in Burkina Faso and South Africa found 94.6% clinical performance for *care HIV* assay compared to HC2 (Kelly; et al., 2021; Ngou et al., 2013) and a sensitivity of 88.8% and 61.8% respectively (Kelly; et al., 2021; Segondy et al., 2016).

Researchers assessed intra-rater and inter-rater consensus to determine the validity of the outcomes in a study assessing *care*HPV assay in Nigeria. The intra-rater agreement for Technicians 1 and 2 were 98.8% and 98.9% respectively, and the inter-rater agreement was 96.3%, indicating that *care*HPV results were credible (Desai et al., 2020). Because molecular assay for HPV does not always require typical cervix samples, another possible advantage is the use of self-collected samples. This could lead to an increase in testing among women, particularly in contexts where self-collection is encouraged, either for cultural reasons or because it is more convenient to provide samples without having to go to a health facility (Saville et al., 2020; Tiiti et al., 2021). This is in line with the recommendation by the WHO which recommends the use of samples self-collected or sampled by healthcare providers among WLHIV (WHO, 2021b). The performance of self-collected samples for HPV diagnosis may vary depending on the type of HPV detection test used and the histological stage of cervical lesions, but additional studies are needed to confirm these findings (Lazcano-Ponce et al., 2017; Lazcano-Ponce et al., 2014). Researchers are also investigating the prospect of developing a molecular HPV testing approach that does not require cervical or vaginal samples. One such test is a urine-based assay, which appears promising but has to be evaluated further (Rohner et al., 2020; Sahasrabuddhe et al., 2014). When Tiran Saucedo (2018) compared urine specimens from pregnant mothers with self-collected vaginal samples, they discovered that the HPV DNA test findings from the urine and vaginal samples were remarkably similar.

Because HPV molecular assays have a stronger negative predictive value, they can help clear up any uncertainty when pap and other tests produce conflicting results. CC screening with HPV testing is a preferred first step. However, these molecular assays can't tell the difference between transitory and persistent infections, their specificity is reduced. Women above the age of 30 or 35 are advised to use them. If the result is negative 12 months after therapy, molecular tests suggest total viral eradication, making them useful for patient follow-up. It has been proposed that all women over the age of 30 who have HPV16 and/or 18 positive results should get a colposcopy right away. Several researches have evaluated several techniques, including those that integrate HPV genotyping and cytology at the same time and others. The results of the "Athena trial" suggested that both strategies are feasible (Castle et al., 2011). Other essential variables in deciding the screening approach used in any scenario include the strategy's capacity to reduce the number of unnecessary colposcopies while retaining a strong "negative predictive value" (Luttmer et al., 2015; Murillo et al., 2021).

Prevention of HPV infection

According to the WHO (2014), effective CC prevention and control methods aim to reduce the burden of the disease by reducing HPV rates, promoting early detection and treatment, and delivering rapid treatment and palliative care. HPV prevention is categorized into primary and secondary preventive strategies.

Primary prevention of HPV: This is described as minimizing the risk of infection by improving infection resistance and so preventing infection (WHO, 2014). Primary prevention of CC involves strategies including abstinence,

condom use, and HPV vaccination (Bruni; et al., 2019a; Steiner et al., 2021). Vaccines against HPV types linked to cancer are perhaps one of the most significant advancements in the prevention of anogenital malignancies (Bruni; et al., 2019a). Since 2007, the introduction of HPV vaccines have had exceptional effectiveness in lowering HPV infection and related clinical problems, including cervical cancer and anogenital warts, as reported in Australia (Bauer et al., 2012; Fairley et al., 2009) and other research (Smith et al., 2015; Wang et al., 2021). Most countries administer the vaccine through the school system to immunize girls before they become sexually active. The bulk of nations that have introduced this vaccination are in the industrialized world, with only a few (15%) in the developing world (Ladner et al., 2014; Mwegoha, 2020). HPV vaccinations have a good safety profile (Stillo et al., 2015; Suryadevara, 2021). A new global analysis of data from over one million quadrivalent vaccine recipients from 2006 to 2015 identified no significant adverse effects (SAE) in those who received the vaccine (Moreira et al., 2016; Sonawane et al., 2021). Presently, available HPV vaccines are aimed mostly at preventing the hr-HPV types 16 and 18 (Giannone et al., 2022). Gardasil®/Silgard® (Merck & Co., Whitehouse Station, NJ, USA) protects against HPP6, 11, 16, and 18, whereas Cervarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium) has antigens for HPV types 16 and 18 (Gupta et al., 2017). A third nano-valent vaccine that was developed and accepted in 2014 employs a similar virus-like particle (VLP) adjuvant system as the quadrivalent and provides protection against HPV6,11,16,18,33,45,52 and 58. These HPV types are said to be responsible for about 90% of cervical cancer cases or abnormalities globally (Joura et al., 2015; Schiller and Müller, 2015).

These vaccines have been determined to be immunogenic and have a low risk of side effects (Paraskevaidis et al., 2020; Sow et al., 2013). Both vaccines are administered in three doses for six months and are well tolerated. Gardasil® was reported to be used in the majority of high-income nations, while the situation in poorer countries was more mixed (L. Markowitz et al., 2012; Runngren et al., 2020).

In 2013, Ghana employed the Gardasil® vaccine for a trial vaccination program (Vodicka et al., 2022). Vaccination for boys has been established in certain industrialized countries, like Australia (Garland et al., 2015; Georgousakis et al., 2012). In their systematic review to assess the population level impact and herd effect of HPV vaccination in developed countries with more than 50% HPV vaccine coverage, Drolet et al. (2015) discovered a 68% reduction in HPV 16 and 18 prevalence, a 61% reduction in anogenital warts in girls 13-19 years.

In studies in diverse socioeconomic circumstances, national-level HPV vaccination for girls has been demonstrated to be a cost-effective method (Novaes et al., 2015; Puliyel, 2021). Several researches have looked into the elements that may influence vaccine tolerance or potency in various circumstances (Verma et al., 2023). Africa is endemic to malaria, HIV/AIDS, and other diseases that interfere with the immune system which may affect the safety and efficacy of HPV vaccines as in the case of the Bacillus Calmette-Guerin (BCG) vaccine are epidemic in Africa (Kaufmann et al., 2014). The concern on how these circumstances which are common in developing nations might impair the efficiency of HPV vaccines has been reported (Lehtinen et al., 2006) . Some studies found no evidence of a decline in HPV

16 or 18 geometric mean titers (GMT) among the vaccinated cohort of girls aged 10 to 25 years over their follow-up period in Tanzania, despite the high frequency of parasitic illnesses, including high malaria parasitemia (10.2%) (Alvarez-Larrotta et al., 2018; Baisley et al., 2014).

The prevention of HPV may also include possible social behavioral ways such as proper sexual behavior patterns, reproductive factors, micronutrient and vitamin supplementation usage, chemoprevention, regular visitation to gynecological clinics, and the use of chemotherapeutic agents. Counseling messages on quitting smoking, using condoms, circumcision, and limiting the number of sexual partners can all assist to lower the risk of cervical cancer. Among men who are circumcised, there is about 80% reduction in the prevalence of CC among their partners (Morris, 2019; Morris and Hankins, 2017).

Also, the chance of contracting HPV and subsequent development of CC among women whose partners use condoms is 80% reduced (Kim et al., 2012; Zidi et al., 2020). There is a reported 20% clearance rate of CIN disease within 2 years in women whose partners use condoms continuously for 6 months (Mantoani et al., 2021; Munk et al., 2012).

Secondary prevention: HPV secondary prevention aids in early disease diagnosis in the early phases of development. The importance of secondary prevention is to identify diseases in their early stages of development, before symptoms emerge, and to stop their progression with less-invasive treatments that increase recovery chances. Given that the formation of precancerous lesions occurs several years before the development and progression of cancer, secondary prevention is optical in CC prevention. .Cytological screening for

precancer identification has helped to reduce cervical cancer incidence drastically in countries that employ them. Also, numerous randomized trials have shown that HPV testing for hr-HPV cervical infection is a viable screening method (Ronco et al., 2014; Thomsen et al., 2015). Cytology is substantially less sensitive than HPV testing for predicting future risk of CIN2, CIN3, and cancer. With a negative cytology test result, due to the negative predictive value above 99%, the likelihood of developing a precancerous within the next five years is almost eliminated (Ronco et al., 2014; Thomsen et al., 2015). But it lacks specificity; a positive result might just signify a temporary infection, which happens often and has no consequences, especially in young women (Kreimer et al., 2013; Rettig et al., 2018). Limiting HPV testing to women from 30 years old and above helps improve specificity, as the infection is less frequent among women of ages below 30 years but more likely to persist and proceed to cancer at the age of 40. In a research by Kreimer *et al* sera of individuals with HPV-driven oropharyngeal cancer demonstrated the presence of HPV16 E6 antibodies (Kreimer et al., 2013; Prétet et al., 2022). Chemotherapeutic agents such as Erlotinib which inhibits epithelial growth factor receptor tyrosine kinase activity immortalize human cervical cells in culture could be a good therapeutic agent against cervical cancer infection (Mongiardi et al., 2021; Woodworth et al., 2011). Similarly, indole derivatives from digested cruciferous vegetables inhibit the transcription of HPV and control estrogen metabolism (Amare, 2020; Rieck and Fiander, 2008). Iota-carrageenan in the food industry is noted to eliminate detectable HPV-infected cells in mouse models and could be explored further

in human trials in preventing HPV infection among humans (Carse et al., 2021; Laurie et al., 2021; Marais et al., 2011).

Tertiary prevention: In addition to preventing or controlling morbidity due to cancer treatment, tertiary prevention also includes preventing cancer recurrence**.** Malignant cells are driven by HPV and display viral DNA sequences, especially the viral oncogenes E6 and E7 (Reder et al., 2020). As a result, the viral antigens that are visible on their surface are targeted by an adaptive immune response (Trimble et al., 2015). These characteristics unique to malignancies caused by HPV may be employed as tumor biomarkers. Antibodies against the viral oncoproteins E6/E7 are frequently found in patients with HPV associated cancers as compared to healthy individuals (Kardani and Bolhassani, 2018). Vaginal and blood biomarkers play a key role in monitoring the resurgence of HPV. Monitoring HPV antibody levels after treatment helps in predicting HPV resurgence (Cutts and Hanson, 2016). A fall in HPV antibody levels was linked to remission whereas persistence signified recurrence or residual disease (Mirghani et al., 2017).

Cervical Cancer

According to estimates, there will be 604,000 new instances of CC and 342,000 cancer-related mortality globally in 2020, making it the fourth most common malignancy and the fourth commonest cause of cancer mortality in females (WHO, 2020b). It is the most often diagnosed and the main cause of cancer mortality in 23 and 36 countries respectively, in SSA, Melanesia, South America, and South-East Asia. (Sung et al., 2021). SSA has a high regional CC prevalence and death rate, with rates also increasing in Eastern Africa, Southern Africa, and Central Africa (Jedy-Agba et al., 2020). Northern

America, Australia/New Zealand, Iraq, and Saudi Arabia had 7 to 10 times lower incidence rates, with fatality rates ranging from 7 to 18 times lower globally (Ferlay et al., 2020). "The International Agency for Research on Cancer Monographs" (Bae, 2021; Ikeda et al., 2021) classifies 12 carcinogenic forms of HPV as group 1 carcinogens, making them a "required but not sufficient" agent for CC (Ikeda et al., 2021). Smoking, having more children, having more births, and using oral contraceptives for an extended period of time are also crucial cofactors, as are some sexually transmitted diseases such as HIV and *Chlamydia trachomatis* (Gates et al., 2021). In LMICs versus developed countries, figures remain excessively high. The human development index (Yousefi et al.) and deprivation indices have been demonstrated to be responsible for more than 52% of worldwide death variance (Singh, 2012). Globally, there has been a decrease in incidence and associated deaths in some countries which are attributed to reasons including rising "socioeconomic levels", improved genital cleanliness, reduced parity, and a lower rates of STIs (Eun and Perkins, 2020), and implementation of "cervical cancer screening programs" (Bray et al., 2020; Eun and Perkins, 2020). In Oceana, the Caribbean countries, Central and Southern America, and Japan, there has been a decline in the rate of CC (Pilleron et al., 2020). Nonetheless, there has been a peak in premature cervical cancer deaths in Central Asia and Eastern Europe due to the absence of effective screening programs in recent times (Bray et al., 2013; Yordanov et al., 2021). SSA, on the other hand, remains the most concerned region as far as cervical cancer is concerned with the Gambia, South Africa, Kenya, Zimbabwe, and Seychelles being the countries with the most reported cases (Jedy-Agba; et al., 2020).

Given the significant worldwide burden of cervical cancer and growing inequality, the WHO made a demand in 2018 to eradicate cervical cancer through a triple-intervention approach of vaccinating all girls of 15 years old, screening for women who are 35 and 45 years twice in a year, and treat at least 90 % of all precancerous lesions de novo (WHO, 2018), until 2059 in countries which are HDI and up to the end of the 21st century in LMIC. .

SSA and Cervical Cancer

Amongst African women, CC is the primary cause of cancer-specific deaths (Cohen et al., 2019). SSA has the world's largest occurrence rates of CC (Ngcobo et al., 2021). In total, 90,000 new infections of cervical cancer are diagnosed annually, with 57,000 fatalities are recorded in SSA (Black and Richmond, 2018). In SSA, CC is a severe health problem for women due to the lack of resources to develop strong screening programs(Sankaranarayanan et al., 2013),. Also, the lack of trained health care personnel to handle HPV and its associated cancer, bad governance, poor economic policies, endemic civil conflict, poor sanitation, HIV/AIDS, tuberculosis, malaria and maternal deaths (Awolude et al., 2013) all contributes to the HPV burden among women in SSA. In Rwanda and Burundi, where the HPV vaccination program covered 89% of young girls, the prevalence of HPV and CC have declined drastically (Baussano et al., 2021). A rich Africa will have the capability and capabilities to concentrate on cutting-edge health services like cancer care and prevention (Cooke, 2010).

Diagnosis of cervical cancers

Cervical cytology

The Lasker prize was given to George Papanicolaou in 1950 for developing the Pap smear test, which has remained a major detection and diagnostic tool for cervical cancer. This entails collecting cells from the transformation zone of the cervix and then staining for cytology analysis under a microscope (Hussain et al., 2020). Dyskaryosis, koilocyticatypia, and dyskeratosis are cellular abnormalities that indicate HPV infection (Vermund and Kelley, 2019). The Bethesda system, which has undergone numerous changes, is used to interpret pap smears. Currently, Pap smears results are classified according to the 2001Bethesda categorization as normal cytology, atypical squamous cells of undetermined significance (ASC-US), high grade squamous intraepithelial lesion (HSIL), low grade squamous intraepithelial lesion (LSIL) (Ruan et al., 2020). The biopsy tissue is stained and reported based on the Cervical Intraepithelial lesions (CIN) classification system, HSIL and squamous cell carcinoma (Ruan et al., 2020). This diagnostic tool however has some challenges. Due to how cells are dispersed across the slides, the 'false negative' percentage ranges from 20-30% (Mahmoud Hagag et al., 2020). Cell clumping, the presence of other bacteria, blood, and other impurities such as yeast cells all raise the chance of "false negative" results (Li et al., 2021; Solomon et al., 2002). Using liquid-based cytology procedures, where cells are collected into a preservative solution, the sensitivity of Pap smear testing can be raised to about 80% for detecting precancerous lesions (Armstrong and Guest, 2020). Another drawback of cytology-based

approaches is that they do not provide a direct test for the virus; instead, they merely provide an indication of the virus's presence (Kannappan et al., 2021).

Colposcopy and cervical biopsy for histopathology

Identifying which women need to have the "cervical transformation zone" destroyed, where recurrent HPV infections can cause cancer, requires colposcopy examination and guided biopsy (Wentzensen et al., 2021). One of the main issues with the entire cervical cancer screening procedure right now is improving the accuracy of colposcopy and biopsy specimens (Redman et al., 2021). Cervical biopsies for histopathology are taken when abnormal cells are discovered during pelvic examination and Pap test respectively (Lakshmi, 2022). Also, a biopsy may be taken after HPV DNA test results. A colposcopy frequently includes a cervical biopsy. This histology approach detects low- and high-grade dysplasia but may miss micro-invasive illnesses (Stuebs et al., 2022). When required, a cervical biopsy is performed and samples are obtained for histology. In underdeveloped countries like Ghana, this necessitates the presence of competent individuals, the colposcope, and electricity, among other problems (Ogbonna, 2021).

Visual inspection with acetic acid and Lugol's iodine

Midwives and other healthcare providers may be educated to do a visual inspection with acetic acid (VIA). This has been effective in permitting screening of women in LMICs (Ajenifuja et al., 2013; Teguete et al., 2012). The appearance of aceto-white opaque lesions is regarded as a positive test after applying (3-5)% dilute acetic acid to the cervix and then performing a naked eye inspection (or using a magnifying glass) of the cervix with a strong light source for about a minute later (Hiremath, 2013). VIA is a quick-to-

implement system that allows for speculum examination and prompt cryotherapy treatment for approved candidates by the same trained professionals (Huchko, 2018; WHO, 2017). Colposcopy and biopsies of aceto-white lesions for histopathology are also possible. It was shown to be a good option in underdeveloped nations when it was applied, particularly as most of these countries lacked the resources required for any other cervical cancer screening methods (Teguete et al., 2012). Since 2001, Ghana has used VIA in a number of pilot sites across the country, and the method has been determined to be feasible and acceptable, though with economic implications for scale-up (Rice, 2019; Wieland et al., 2014). In women with a high cervical squamous-columnar junction, however, VIA has limits because it does not allow for a full evaluation of the junction and can result in incorrect results. In postmenopausal women, interpreting results is also difficult. Several studies have revealed that cytology has a similar sensitivity to molecular approaches but is less specific (Akpabla and Sun, 2021; Teguete et al., 2012), and performance might be poor depending on the quality of training. Visual examination with Lugol's iodine (VILI) is an alternative to VIA Lugol's can be used instead of or in addition to acetic acid (Huchko et al., 2015; Raifu et al., 2017). It's done the same way, with the reading taking place one minute after the iodine has been applied. Positive lesions in the cervix appear mustard yellow on examination, which may provide better contrast for some readers (Raifu et al., 2017). The issues are similar to those faced by VIA. Simple, low-cost, and time-efficient testing are benefits of both single and combined tests, allowing localization to basic health care clinics and paramedical staff (Huchko et al., 2015).

Potential biomarkers

Several novel molecular biomarkers are being studied as potential cervical neoplasia screening tests (Kori and Yalcin Arga, 2018). The p16INKa gene is one such marker. This is a surrogate marker for hr-HPV transforming activity because it inhibits cyclin-dependent kinase (Halec et al., 2017). p16INKa is overexpressed in cervical neoplasia, hence, it is being studied as a prospective diagnostic marker (Kori and Yalcin Arga, 2018). Immunohistochemistry for p16INKa is thought to reduce the human factors in interpreting cytology data as well as histopathological diagnosis (Ding et al., 2020; Gashi et al., 2018; Muvunyi et al., 2021). p16INKa is an appropriate marker for cervical disease because women with cervical lesions but negative for p16INKa tend to revert to normalcy , whereas those positive for p16INKa advance to invasive CC (Albayrak et al., 2021; Ding et al., 2020). As a result, while these tests have a lower sensitivity, they have a greater specificity when compared to HPV DNA molecular testing (Muvunyi et al., 2021). Also, because *E6 and E7* proteins are critical in the development of cervical cancer, identifying over-expression of these genes in the cervix epithelium could distinguish between women with transient or clinically insignificant HPV infection and those with substantial cervical lesions (Reder et al., 2020). As a result of the high specificity and positive predictive values demonstrated by some of these E6 and E7 assays (Salimović-Bešić et al., 2019; Salimović-Bešić et al., 2013), these assays may be used to screen for cervical lesions in women without incurring the additional cost of HPV DNA detection and reducing the need for colposcopy. Similarly, a brief measurement of cancer antigen 125 (CA-125) and insulin-like growth factor 2 (IGF-II) proves useful

in the diagnosis of cervical cancer (Chrisostomos et al., 2020; Tornesello et al., 2013), while the detection of cancer antigen 19-9 (CA 19-9), vascular endothelial growth factor (VEGF), and interferon gamma (IFN-γ) proved significant diagnosis of "cervical cancer" (Laengsri et al., 2018).

An essential element of the Erbb pathway, Epidermal growth factor receptor (EGFR), is abnormally active in several malignancies (Arienti et al., 2019). Phosphorylation of EGFR promotes a variety of "pro-carcinogenic signaling pathways", most notably the "ERK and PI3K/AKT pathways" (Adiga et al., 2021). In cancer, abnormal Erbb signaling enhances "growth, migration, angiogenesis, apoptosis suppression, and irradiation resistance" (Seshacharyulu et al., 2012). EGFR upregulation is reported to be associated with CC progression, spread, and poor outcomes in several studies (Arienti et al., 2019).

Overall, the discovery of molecular biomarkers through genomic and proteomic research has unveiled new features for illness classification and therapies, paving the way for personalized medicine. An increased EGFR level has been associated with tumor growth, LN metastasis, and disease relapse (Soonthornthum et al., 2011). Cytoplasmic p-EGFR staining and membrane-forming EGFR staining have been found to be independent predictors of poor response to chemoradiation (Iida et al., 2011; Soonthornthum et al., 2011). PAR2 (Protease-activated receptor 2) and EGFR overexpression have been linked to cisplatin resistance (de Almeida et al., 2018).

Challenges associated with Cervical cancer screening

Very few LMICs have so far been successful in putting CC screening programs into place (Modibbo et al., 2016). Different conditions are crucial

for LMIC screening to be successful. The program must offer comprehensive coverage of the target population, patient screening, management, and proper follow-up, on-site delivery at a cheap cost with the bare minimum of infrastructure requirements, and quick treatment in the event of abnormalities. Less than 5% of women who are at risk have ever had a screening in SSA (Adefuye et al., 2013). The screening coverage is still extremely poor, despite the implementation of these national guidelines (Aswathy et al., 2012). Several issues prevent LMICs from implementing a successful screening program. In Thailand, self-collection for cervical cancer screening was found to be an acceptable and realistic approach (Tan, 2020; Trope et al., 2013). Other research have used real-time PCR tests to evaluate self-collected vaginal samples (Rai et al., 2014). Lack of awareness about cervical cancer and the various screening technologies has also been noted as a barrier to screening in underdeveloped nations (Ebu et al., 2014). This low level of awareness has been reported among various women in Ghana. (Ebu, 2018; Ebu et al., 2015).

In Ghana, cervical cancer screening faces numerous hurdles. These issues include the scarcity of screening locations and the high cost of screening (Pap smear or VIA) (Asgary et al., 2019). When it comes to molecular-based screening technologies, which are exclusively available in research institutions, the situation is even worse (HPV detection and genotyping) (Anaman-Torgbor et al., 2020). The reliance on clinician-collected cervical samples is another challenge for cervical cancer and HPV screening programs in such socio-cultural settings (Asare et al., 2022). For a variety of reasons, this may reduce acceptability and thus screening coverage (Obiri-Yeboah et al., 2017). The busy lives of women in the industrialized

world could be one of the reasons, as they may not want to take time out of their schedules to travel to the hospital to have their samples collected. The situation becomes more complicated due to Africa's numerous cultural diversities, particularly in Ghana (Obiri-Yeboah et al., 2017). Women in Africa have cultural views that may influence the technique of sampling, whether done by a female or, worse, a male health worker. In a recent study conducted in Ghana, it was discovered that another obstacle to CC screening among Ghanaian women is the cultural belief that it is unacceptable for someone else to see a person's genitals (Banza et al., 2020; William et al., 2013). Various researches have proven that the self-collection of cervical samples by women improves cervical screening participation (Hawkes et al., 2020; Saville et al., 2018). In the USA, self-collected HPV testing has previously been reported to be extremely acceptable among HIV-positive women (Wang, 2020), and positive test findings enhanced their assessed risk of cervical cancer (Mabeya et al., 2012). Similarly, in Ghana, Obiri-Yeboah *et al.,* found out that about 61.9% of Ghanaian women think self-collection of vaginal samples will improve participation in CC screenings, while 76.3% felt self-collection of vaginal samples was convenient and approximately fifty eight (57.7%) prefer self-collection to clinician collection of samples (Obiri-Yeboah, 2017). In a study conducted in Ghana comparing the HPV genotyping with *care*HPV, a qualitative HPV DNA assay proved that *care*HPV has 94.3% concordance with full HPV genotyping for 14 hr-HPV genotypes (Obiri-Yeboah, 2017)

The challenges faced with CC screening among WLHIV in LMIC could be attributed to poor knowledge of sexual transmission of HPV and the

late diagnosis of HPV (Adedimeji et al., 2021). Inadequate health facilities for cervical cancer screening hinder screening success among WLHIV (Adedimeji et al., 2021). Also, HIV-associated stigma presents a major challenge to HPV since WLHIV are unwilling to partake in CC screening programs that are integrated into HIV programs. (Guillaume et al., 2020). In most LMICs, factors such as shortage of qualified health personnel, poorly equipped facilities, and the cost of screening further hinder WLHIV to screen for CC (Adedimeji et al., 2021).

Cervical cancer prevention and management

Primary prevention of Cervical Cancer:

The global prevalence of HPV infection demonstrates that it is a huge public health concern. Preventive interventions must be comprehensive. The evolutionary history of HPV infection allows for mediation to either prevent HPV infection from occurring in the first place or to detect intraepithelial cancer precursors before invasive illness develops, followed by appropriate therapy. The most efficient preventive method for HPV infection is the use of prophylactic vaccination, however, lifestyle changes are also important and should be encouraged (Anand et al., 2008). These generic measures will improve sexual and general health while lowering the risk of HPV infection in the community (Pierz et al., 2021). Health promotion techniques such as sexuality education, lifestyle adjustment, anti-smoking campaigns, preventing early sexual debut, etc should be employed together with other preventative strategies. Since 2006, three preventive HPV vaccines were developed, evaluated, and licensed in more than 100 countries(L.E. Markowitz et al., 2012) . These vaccines were included in national vaccination programs in

developed countries. In women under the age of 26, both vaccines have been demonstrated to reduce nearly 100% of persistent HPV-16 and HPV-18 infections as well as the associated lesions (L.E. Markowitz et al., 2012). (Joura and Pils, 2016). The third vaccine, the nano-valent HPV vaccine provides a 99% reduction in sero-convention or HPV acquisition rate (Joura and Pils, 2016). It provides protection against HPV genotypes 6,11,16,18,33,45,52 and 58 (Joura et al., 2015). Overall, all three prophylactic HPV vaccines have been proven to be effective (Yousefi et al., 2022).. There is limited data on the effectiveness of the HPV vaccine in HIV-positive persons (Denny, 2012; Hendrickx et al., 2021).

Secondary Prevention of Cervical Cancer:

Secondary prevention is defined as the early discovery and treatment of illnesses by actions such as screening. The severity of the dysplasia or CIN is classified using cytology as mild (CIN1), moderate (CIN2), or severe (CIN3) (L. Denny, 2012). VIA on the other hand, is based on acetic acid, and it allows a health care provider to physically inspect aberrant cellular alterations. Secondary preventive measure employs cytology with colposcopy in confirming abnormal smears followed by treatment. In SSA, this has shown to be unsustainable due to high costs (Muwonge et al., 2009). VIA/VILI has been considered an alternative screening method for most LMICs which has helped in reducing cervical cancer cases in underdeveloped countries (Gallay et al., 2017).

Management and Treatment of Cervical Cancer

Cervical cancer prevention and management procedures have been established and advocated in various ways. These procedures take into account

aspects such as HIV prevalence in the population (Awolude et al., 2013; Greene et al., 2019), as well as the availability of screening and treatment skills, equipment, and resources. Patients with the "International Federation of Gynecologists and Obstetrics (FIGO) stage IA1" illness are identified based on a procedure that does not result in cauterized margins, which might hide surgical margins (Kesic, 2006).. Conservative hysterectomy or conization is employed when women prefer to keep their fertility (Bekkers et al., 2002). In some cases, drastic surgery or radiation is recommended if IA1 is present. FIGO stage IA2, IB1, and IIA are better treated with radical hysterectomy in healthy patients as it preserves ovarian function. Patients with early-stage cancer are effectively managed using radiotherapy (Pierorazio et al., 2021). Primary surgery and radiotherapy are shown to be effective in managing the IB-IIA stage of cervical cancer development (Alagoda et al., 2021; Zhu et al., 2021).

Chemoradiotherapy is shown to improve survival and survival more than radiation alone in patients with stage IIB, II, IVA, and IB2 illnesses (Sanders et al., 2021; Singh et al., 2022; Weiping et al., 2020). For these patients, platinum-based chemoradiotherapy is currently the mainstay of treatment (Pierorazio et al., 2021). Among women with FIGO stage IB2 cervical cancer, the addition of cisplatin to pelvic radiotherapy before hysterectomy minimizes the recurrence of disease and mortality among women compared to radiotherapy and hysterectomy alone (Stanca and Căpîlna, 2021). The European Organization for Research and Treatment of Cancer is now investigating the role of neoadjuvant chemotherapy followed by major surgery in managing these stages of the disease.

In patients with stage IVB illness, therapy is only palliative, hence the quality of life and tolerability characteristics must play a role in drug selection. Cisplatin was compared to cisplatin + topotecan in the only RCT to find a chemotherapy regimen that offered these patients an overall survival benefit and included quality of life measurements (Braz et al., 2021; Petignat and Roy, 2007; Remick et al., 2020). Combination chemotherapy favored progression-free survival and overall survival, although toxicity was more likely, albeit it did not significantly affect the quality of life (Conway et al., 2020; Wiltink et al., 2020). Follow-up helps detect recurrence early enough for salvage treatment as well as evaluate and manage treatment-related toxicity (Conway et al., 2020). The majority of recurrences happen within the first two years of main therapy. Physical examinations such as rectovaginal examination, nodal evaluation, and cervical smears are employed in managing the recurrence of infection. It is advised that physical examination in the first three years should be done every three to four months (Melamed et al., 2018; Petignat and Roy, 2007), and every six months after the fifth year. Pain, vaginal bleeding, and gastrointestinal or genitourinary problems are checked for regularly (Aoki et al., 2018; Wiltink et al., 2020)

The screen-and-treat protocol, for example, states that women are screened with HPV DNA testing or other methods like cytology VIA, and all positive women are treated with cryotherapy right away (WHO, 2021a). In a studies among WLHIV in Cape Town, South Africa and in Bangladesh, it was found that screening and treating with HPV DNA testing was more convenient and effective in reducing cervical cancer precursors than it was with VIA and cytology (Devine et al., 2021; Singh, 2021).

Cervical Cancer and HIV

HIV

HIV is a retrovirus that uses the reverse transcriptase protein to multiply via a DNA precursor. HIV-1 and HIV-2 are the two varieties, with type 1 accounting for most infections in many parts of the world, including Ghana (Addo et al., 2014). The majority of adult HIV-1 infections still occur through heterosexual transmission, which accounts for around 85% of all HPV and HIV-1 infections (Simon et al., 2006). Three to six times as many female adolescents as male adolescents get HIV-1, and this gap has been linked to several factors, including biological, socioeconomic, and behavioral ones (Karim and Karim, 2002; Simon et al., 2006).

The virus interacts intensively with the infected person's immune system, resulting in the progressive elimination of naive and memory CD4+T-lymphocyte populations (Pallikkuth et al., 2016). The virus attaches itself to host cells by engaging with co-receptors via the envelope glycoprotein gp120. It subsequently enters the cell and releases the RNA into the cytoplasm, where reverse transcription takes place, resulting in the production of a DNA copy. This circular DNA copy penetrates the cell's nucleus and is put into the host cell's DNA.

The host RNA polymerase then initiates transcription, resulting in the synthesis of viral mRNA. Protein synthesis results in the formation of a polypeptide, which is then translated to create virions, a stage in which the protein synthetase enzyme is involved. The virions obtain envelope and core proteins, as well as mature virion buds, from the host cell, which is normally accomplished through lysis of the host cell.

Epidemiology of HIV

Notwithstanding the massive efforts put in globally and regionally to eradicate HIV and "Acquired Immune Deficiency Syndrome (AIDS)" persist as a substantial worldwide health crisis (Chin, 2007). In resourced constraint countries, the HIV epidemic is widespread, well-grounded throughout the entire populace, and transmitted wildly among heterosexuals and also through mother-to-child. However, in developed or advanced countries, the HIV epidemic is somewhat limited to men who sleep with men (MSN), migrants, and intravenous drug users (Porter et al., 2018).

In 2019, there were 36.9 million instances of the HIV/AIDS epidemic globally, representing 0.5% of the world's population, with a prevalence rate of 476 cases per 100,000 people (Govender et al., 2021). The pandemic reached its peak in 2005, then began to fall for five years before starting to rise again in 2010. (Govender et al., 2021). (Swanevelder et al.),Spain, Germany, Spain, Peru, Brazil, Mexico and the United States of America all reported an increase in frequency of HIV (Govender et al., 2021). These nations are seeing greater growth than would be expected from population increase alone, as evidenced by the fact that both the gross and age-standardized rates are growing (Govender et al., 2021). The incidence rate in Portugal increased quickly between 1990 and 2019, ranging from 86 to 370 per 100,000 persons (Govender et al., 2021; Porter et al., 2018). This, however, comes nowhere close to South Africa's spectacular rise from 354-14,251 per 100,000 within the time frame (Govender et al., 2021).

In the USA, there has been an increase in incidence from "15.6 fresh cases per 100,000 in 2010 to 21.0 new cases per 100,000 in 2019" (Govender

et al., 2021). Nonetheless, from 2010 to 2019, there has been a rise in new infections from 48,175 in 2010 to 67,000 in 2019 and for more than a decade, this rise has been consistent in the US (Govender et al., 2021). Similarly, in Ukraine, Russia, Brazil, and Portugal, the rate of rising of new cases has been alarming, however, there has been a decline over the last five years in Ukraine and Russia (Govender et al., 2021).

The prevalence of HIV in adult population in SSA declined by half between 2000-2012 and this to a decline in new cases reported in 2012 by approximately a million (UNAIDS report on the global AIDS epidemic, 2014). Multiple sex partners and concomitant sexually transmitted infection, primarily herpes simplex type-2 (HSV-2), enhance the risk of transmission (Chen et al., 2007; Nabukenya et al., 2020). Long-term heterosexual partnerships may be responsible for an elevated proportion of fresh HIV infections. At least two-thirds of HIV-positive couples in SSA are in discordant partnerships (Eyawo et al., 2010; Rouveau et al., 2021). In Zambia and Rwanda, about 95% of persons living with HIV live with their partners (Ntaganira et al., 2009). Prevalence of HIV among MSM in studied communities has spanned from 14% in Uganda, to 17% in Botswana, Malawi, Namibia, and Nigeria, and up to 50% in Johannesburg, South Africa (Wariki et al., 2013). SSA is home to about 88% of all HIV-positive children (UNAIDS report on the global AIDS epidemic, 2014). Children, on the other hand, have less access to ART than adults, with just 28% of children in SSA obtaining the therapy (Sutcliffe et al., 2008) Central and south African nations have been deeply affected with the burden of HIV/AIDS (Govender et al., 2021). There is no one explanation for the devastating outbreaks of HIV in

SSA, however, the high HIV load may be due to a combination of high HSV-2 rates, poor male circumcision rates, and sexual risk factors such as many partners and intergenerational sex, as well as big migrant populations (Hendrickx et al., 2021; Orroth et al., 2007). New infections have continued to fall across the sub-region. In Eastern Africa, HIV prevalence is lower than in Southern Africa, with rates ranging from 2.9% in Rwanda to 7.2% in Uganda (Rouhani et al., 2017). Except for Uganda, where HIV incidence grew during the late 2000s, this region's incidence and AIDS-related mortality are likewise decreasing (Rouhani et al., 2017).

HIV prevalence in Western Africa spans from about 1.3% in Gambia to 3.2% in Cote d'Ivoire (Rouhani et al., 2017; UNAIDS, 2013b). Nigeria (3.4 million PLHIV) has the highest estimated number of PLHIV in West Africa, with an HIV prevalence of 3.1% and AIDS-related fatalities continuing to rise (Sam-Agudu et al., 2017). The Prevalence of HIV(Rouhani et al., 2017) in Central Africa is similar to that of Eastern and Western Africa, ranging from 1.1% in the Democratic Republic of the Congo to 4.5% in Cameroon, with a decline in the incidence and mortality of AIDS in the Central African Republic (Rouhani et al., 2017).

Asia has the second highest burden of HIV after SSA. However, just as in Africa, HIV prevalence is declining in Asia; nevertheless, the epidemiologic differences in the two regions are enormous. Despite lower HIV transmission rates, the number of PLHIV has risen due to improved survival. The high-risk groups for HIV transmission include MSM, injection drug users paid sex workers, and plasma donation through contaminated equipment (De Cock et al., 2012; Kabapy et al., 2020). AIDS-related fatalities among adults and

children in Asia have steadily decreased since the early 2000s, down from a peak of 330,000 in 2005 to around 260,000 in 2012 (Granich et al., 2017) with the largest illness burdens in China and India. About 2.1 million of PLHIV reside in India, the highest in Asia (Paranjape and Challacombe, 2016). Nonetheless, the 0.3% prevalence recorded among individuals between age 15 to 49 ranks India lowest compared with figures obtained in nations in the region such as Cambodia (0.8%), Myanmar (0.6%) etc. (Granich et al., 2017). Other countries with comparable or lower estimated adult HIV prevalence than India are Laos (0.3%), Nepal (0.3%), the Philippines (0.1%), and Pakistan (0.1%). (UNAIDS, 2013b). HIV prevalence varies greatly by location in India, with HIV prevalence being around 5 times higher in the southern states than in the northern ones. (UNAIDS, 2008).

Between 2000 and 2012, the projected number of PLHIV climbed from 130,000 to260,000, AIDS-related fatalities went from 7300 to17,000, and new infections increased from 20,000 to32,000 every year (UNAIDS, 2013b). AIDS-related infections and mortality among youngsters have also increased (UNAIDS, 2013a; Wariki et al., 2013). In comparison to SSA, HIV prevalence is lower in North Africa and the Middle East (UNAIDS, 2013a). The low HIV incidence in North Africa and the Middle East is largely due to nearly universal male circumcision and lower rates of sexual risk behavior (Akala and Semini, 2010; Mumtaz et al., 2014). Despite the low prevalence, the rising rate of AIDS-related death in North Africa and the Middle East implies an insufficient HIV response (Haroun et al., 2016). The disparity is much more pronounced among children in need of ART, with just 6% receiving therapy. In North Africa and the Middle East, about half (47%) of

PLHIV are informed of their status with 22% having suppressed viral load (Marsh et al., 2019).

Ghana is a LMIC in the Western part of Africa with a 30 million population, $37.86 GDP and a 3.9% GDP growth. (World Bank, 2016). Ghana's 2016 to 2020 National HIV/AIDS Strategic Plan contained the "treat all" policy (Ghana AIDS commission, 2016). The implementation of "treat all" necessitates the improvement of the country's health infrastructure to link and monitor HIV-positive clients so that they may be treated right away. However, reliable figures on the HIV care cascade, such as the percentage of individuals who underwent testing for HIV, the number of people diagnosed positive, HIV-positive individuals who commenced medication, people who had very low viral loads, and t people who continued care is scarce (Ghana AIDS commission, 2016). However, there are few accurate statistics on the HIV care cascade, including people who underwent testing for HIV, people who tested positive, HIV-positive individuals who began treatment, individuals who were virally suppressed, and the number of individuals who continued care.

HIV prevalence in female sex workers (FSWs) was 6.9% in 2015 (Ali et al., 2019) and 18.1% in MSM in 2017 in Ghana (Ali et al., 2019). FSWs and MSM and their clients, are responsible for 28% of all new infections in Ghana (Ali et al., 2019; Gyasi and Abass, 2018). The “Ghana Demographic and Health Survey”, Ghana’s primary source of HIV data, excludes key populations (KPs) (Ghana Statistical Service 2015) and there is no information on the number of HIV-positive KPs linked to care and treatment. In Ghana, several factors hinder KP’s from receiving HIV testing as well as stigma and prejudice at the community and facility levels, inadequate HIV test kits , and

gender bias in testing, which favors women over males (Goosby et al., 2012). If KPs test positive, stigma and prejudice within the facility impede them from receiving regular care. (Laar and DeBruin, 2017). Also, there has been a rise in the adult population on ART in Ghana from 3,663 in 2005 to 119,165 in 2017 (Laar and DeBruin, 2017).

Clinical staging of HIV infection

Acute HIV infection symptoms are vague but include lethargy, rash, headache, nausea, night sweats, and so on. The WHO groups HIV infection into four phases that lead to AIDS.

- **Clinical Stage I:** this clinical stage is defined by asymptomatic HIV infection and prolonged widespread lymphadenopathy.
- **Clinical Stage II:** this stage is characterized by repeated respiratory tract infections, mouth ulcers, *Herpes zoster*, and popular pruritic eruptions.
- **Clinical Stage III:** in this stage of HIV infection, chronic oral candidiasis, pulmonary tuberculosis, severe bacterial-associated infections such as pneumonia, empyema, meningitis, lymphoma, etc occur.
- **Clinical Stage IV:** This stage is characterized by HIV wasting syndrome, recurrent pacterial pneumonia, Kaposi sarcoma, extrapulmonary tuberculosis, chronic herpes simplex infection, esophageal candidiasis, pneumocystis pneumonia, invasive cervical carcinoma, invasive cervical cancer, CMV infection, central nervous system toxoplasmosis, etc.

Management of HIV infection

Over the past three decades, there has been an intense change in the clinical face of HIV epidemic. Over the last two decades, HIV programs have been ramped up over the world, making highly potent antiretroviral medication widely available (HAART). Despite significant progress in the global HIV response, there are still significant gaps in program implementation and HAART access (Marsh et al., 2019; Porter et al., 2018). The initiation of ART is dependent on the CD4 values of patients. Hence, CD4 T-cell counts provide guidelines for the start of ART. The introduction of triple therapy, which consists of a dual NRTI backbone paired with a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor, transformed the prognosis of HIV substantially, as the risk of resistance-inducing mutations was drastically reduced (Vella et al., 2012). The broad use of HAART, which now includes new categories of medications with less adverse effects and a greater genetic barrier to resistance, has culminated in HIV-infected people on suppressive HAART living nearly normal lives (Bianculli et al., 2020). Lundgren et al. (2015) have found that antiretroviral therapy has enormous mortality benefits at all CD4 counts (Lundgren et al., 2015; Venkatesh et al., 2021). Also, among treatment naïve patients, plasma viral loads decline below assay detectable levels in global clinical use with present antiviral regimens (Chen, 2020; Richterman and Sax, 2020; Sax et al., 2009).

HPV and HIV Interplay

HIV clients who are immunosuppressed have a higher prevalence of HPV as well as being resistant to HPV-related illness treatment and are more

likely to acquire HPV-associated cancer (Rodriguez et al., 2021; Ruffieux et al., 2021). HIV has been linked to HPV infection and morbidity across several research. "Syphilis, herpes simplex virus (HSV)-2, *Neisseria gonorrhea, Chlamydia trachomatis, and Trichomonas vaginalis"* are only a few of the frequent sexually transmitted illnesses that have been associated with a high risk of HIV infection.

Both HPV and HIV-1 have been classed as carcinogens by the "International Agency for Research on Cancer" (IARC), and studies have shown that HPV is a primary carcinogen and HIV-1 is a secondary carcinogen via immune suppression (Castle et al., 2021; Clifford et al., 2021). HIV and acquired immunodeficiency syndrome (AIDS) patients are at an increased risk of HPV-associated malignancies (Clifford et al., 2018; Rositch et al., 2021). In the age of ART, the incidence of HPV-related illnesses has continued to grow, but the incidence of several HIV-associated comorbidities has reduced (Lekoane et al., 2020; Mbulawa et al., 2021). Although there are few therapeutic options for HPV-related infections in HIV-positive patients, there are ways to avoid the disease through vaccination. HPV-associated malignancies remain in HIV-infected people despite apparent immunological reconstitution with ART (Vivanco and Mellinghoff, 2010; Yap et al., 2013), emphasizing the significance of improving screening. . The number of women living with HIV ranges from fewer than 1000 cases in Comoros to 3.2 million in South Africa (Finocchario-Kessler et al., 2016) and have a two- to 22-fold increased risk of getting CC compared to HIV-negative women (Bosch et al., 2013; de Sanjose et al., 2018). A study of 1409 males who had sex with men (MSM) in the United States found that having an HPV infection doubled the

likelihood of HIV seroconversion (Al Bitar et al., 2021; Brown et al., 2018). After accounting for sexual activity, the prevalence of additional STIs, and demographic factors, the link remained. Similarly, the link between HPV and HIV infection was investigated in a randomized clinical trial involving 2168 young men in Kenya who were infected with HPV and circumcised. It was found out after week 42 that HPV infection risk is independently linked to an elevated risk of HIV infection, with a cumulative incidence of 5.3% in HPV-positive men as against 4% in HPV-negative men.

Also, HIV positivity has been shown to increase the incidence of cervical HPV infection (De Vuyst et al., 2013; Torre et al., 2016) and "cervical intraepithelial neoplasia (CIN)" (Alshehri et al., 2021) recently. This study reported that women with HIV in South Africa had a greater risk of CIN than HIV-negative women (Alshehri et al., 2021). Transversal case-control studies conducted in Benin that focused on HIV and HPV-related cancers and sought to compare the HPV genotypes of women with HIV who were receiving ARV treatment to those of women who were not HIV-positive also supported this conclusion. (Capo-Chichi et al., 2016; Dlamini et al., 2018). Similarly, in HIV-positive men and women, studies have revealed a significant frequency of anal HPV infection, anal precancerous lesions, and anal malignancy (Dlamini et al., 2018). Anal cancer caused by HPV is increasing amidst ART, has been reported despite the paucity of data on the prevalence of anal cancer in HIV-infected men and women in LMICs (Du, 2019). Other HPV-related malignancies, such as oropharyngeal cancers, have been associated with HIV infection (Jedy-Agba et al., 2016; Lekoane et al., 2019). In addition, HIV-infected persons appear to have an incidence of

oropharyngeal cancer that is two to four times greater than that of HIV-uninfected people (Du, 2019; Firnhaber and Wilkin, 2012). According to a study, five HIV-infected women in Benin had LSIL and one had HSIL (Capo-Chichi et al., 2016; Menon et al., 2017), while another research in South Africa found that 35% of HIV-infected women had LSIL and 13% had HSIL (Bogale et al., 2020). In HIV positive women, the prevalence of LSIL and HSIL has been recorded as 28.6% and 14% respectively in the UK (Lekoane, 2020), 15.4% and 7.9% respectively in the US (Malik et al., 2021), and 21.0 and 2.8% respectively in a European cohort (Zang and Hu, 2021). According to several research HIV positive women had various Hr-HPV genotypes (Bogale et al., 2020; Capo-Chichi et al., 2016; Castle et al., 2021). Persistent HPV types were found to be 24% in HIV-positive women against 4% in HIV-negative women (Lekoane et al., 2020).

Chapter summary

This chapter presents a comprehensive analysis of the literature on the life cycle, epidemiology and pathogenesis of HPV. The research has established a strong association between HPV and CC, highlighting the epidemiology of hr-HPV types that are responsible for the development of CC among women, particularly those living with HIV. Additionally, the current prevention and treatment protocols for the circulating hr-HPV types linked to CC have been well documented.

CHAPTER THREE

METHODOLOGY

Introduction

This chapter describes the study design, study site, sample collection and processing procedures, molecular assays used in the detection of hr-HPV DNA and the statistical tool employed in analyzing the data. It also defines the inclusion and exclusion criteria, the ethical approval obtained for the study, consent agreement with the study participants, and a chapter summary.

Schematic Representation of the Research Methodology

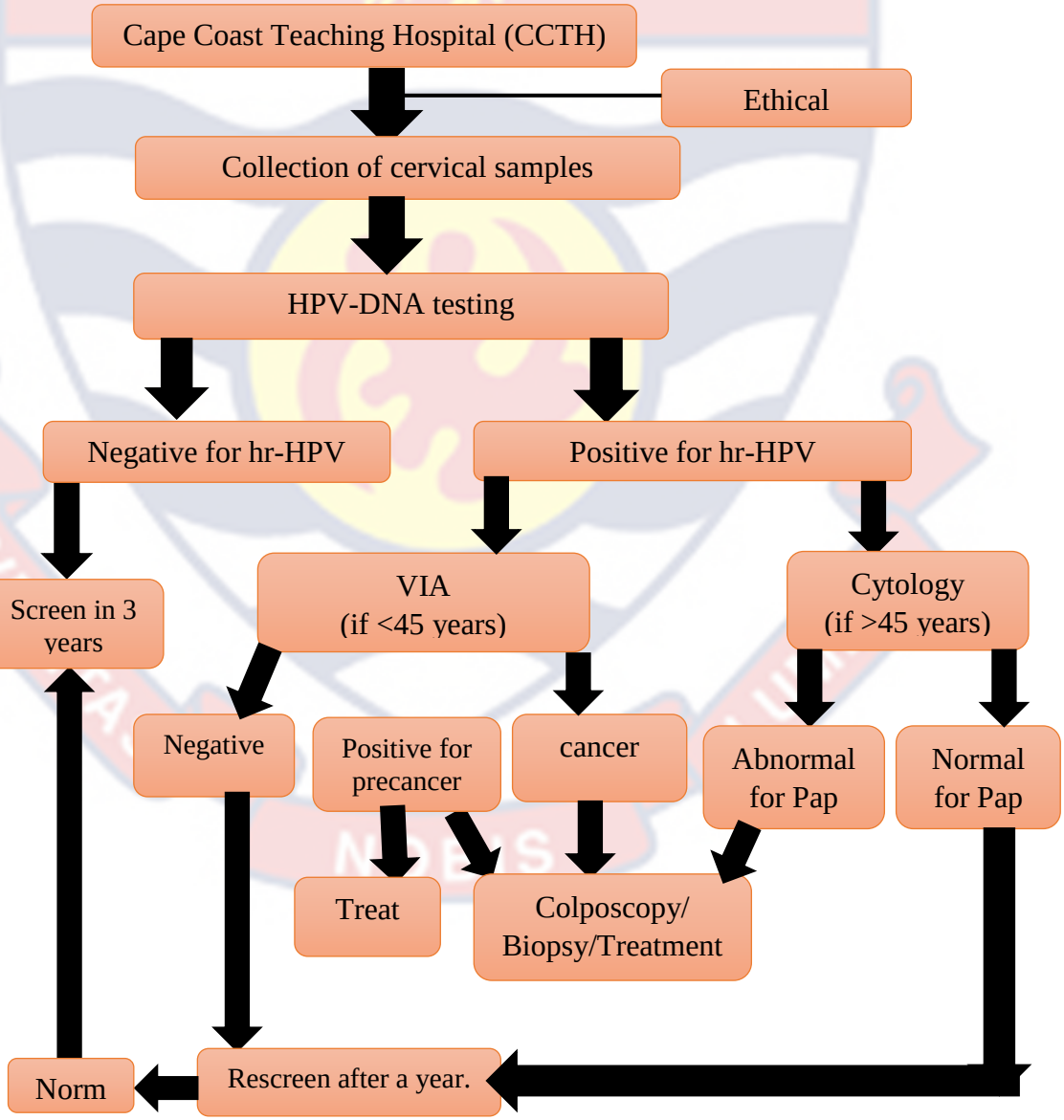

Figure 2: **Algorithm of the Research Methodology**

Study Design

This is a hospital-based cross-sectional study comprising WLHIV and seeking health care at the antiretroviral therapy clinic at the Cape Coast Teaching Hospital (CCTH), Ghana. Cervical samples were self-collected by the study participants and screened using Polymerase Chain Reaction (PCR) molecular technique for hr-HPV screening among WLHIV.

Study site

The study was conducted at the antiretroviral clinic of the Cape Coast Teaching Hospital, Ghana. This health facility serves the health needs of the people of the Central and Western regions of Ghana and also serves as a referral facility in the southwestern part of the country. Cervical samples were screened at Pathology Without Borders Laboratory in Accra, Ghana for hr-HPV genotypes among WLHIV using Atilla biosystems' AmpFire system.

Sampling Strategy and Procedure

A simple random sampling method was used in selecting study participants. Women were asked to pick from a box with papers having a "yes" or a "no" written on them. Recruitment of WLHIV was done on Thursdays at the ART clinic for 4 months, from November 2020 to February 2021.

Inclusion criteria

Women 25 years and above who are positive for HIV (WHO, 2020a) and have not had treatment for cervical lesions or hysterectomy were included in the study.

Exclusive criteria

WLHIV who were pregnant, or have had treatment for cervical lesions/hysterectomy, or menstruating at the time of recruitment, or had never had peno-vaginal sex were excluded from the study.

Ethical consideration, patients' consent and Covid protocol

Ethical approval was sought from the Cape Coast Teaching Hospital Ethical Review Board (CCTHERC/EC/2020/111). In addition to this, an inscribed notified agreement was reached with every project participant who willingly agreed to be part of the study and met the inclusion criteria. Participants were made to know participation was voluntary and one could opt out of the study without it affecting the treatment they will get as HIV/AIDS clients of the facility or the HIV/AIDS service providers. Confidentiality and anonymity were ensured by the use of unique pathological numbers generated for each participant. All efforts were made to ensure sample collection and all research-related activities were carried out as planned. All COVID protocols were duly adhered to during the sampling process. Surgical nose masks and sanitizers were made readily available at the sample collection point for all study participants. Provisions were made for hand washing of both study participants and medical staff to help reduce possible transmission of the covid-19.

Sample size

The minimum sample size was determined by the formula

$S_T = A / [1 + (A-1)/T]$

Where

A is given by $[Z^2*P*(1-P)] / C^2$;

P=Prevalence of the condition

T = Total population at the ART clinic (2,106)

Z = Z value (1.96 for 95% confidence)

P, 60.6% is the prevalence of hr-HPV among HIV seroprevalence women ≥18 years (Obiri-Yeboah. et al., 2017).

E, 5% is the margin of error

Contingency, 5%.

The total sample size (S_T) = 313

Therefore, a minimum sample size of 313 was recruited for the study.

From the sample size calculation, a total of 330 participants was recruited for the study giving a 5% provision for contingency.

Data collection instruments

The data collection tools or techniques utilized for this study include; structured pre-test questionnaires for collecting the socio-demographics of study participants, their knowledge about HPV, their knowledge about cervical cancer, its diagnosis, prevention/treatment, and their reproductive health and other characteristics. The questionnaire is inserted in the appendix. Also, an AmFire HPV detection technology (*Atila Biosystems, Mountain View, CA, USA*) (Zhang et al., 2020) for hr-HPV screening was used. The Atilla biosystem AmpFire system is a molecular technique which is a sensitive method for detecting the DNA of the various hr-HPV through amplification and replication of the organism's genome using specific primers with the help of a thermocycler (Acheampong et al., 2021).

Collection of Cervical Samples

Using the cyto-brush, a recognized self-sampling tool, cervical samples were obtained. Following the manufacturer's directions, cyto-brush samples were self-collected or obtained with assistance from a qualified nurse or gynaecologist. Samples were stored dry at an ambient temperature in water-proof containers and transported to the Pathology laboratory. Each sample in the water-proof container was clearly labelled with the patient's details to avoid clerical errors. Samples were stored at -20^{o}C.

Laboratory analysis

Preparation of 1X lysis buffer from 20X stock lysis buffer and Master Mix

Lysis buffer (BD Biosciences, Pham lyse) and master mix were prepared according to the manufacturer's instructions (appendix).

Sample processing, DNA Amplification and HPV genotyping

Samples were removed stored at -20^{o}C were thawed to room temperature. The brush heads were removed into a 5ml sample tube and 1ml of the 1X LB was pipetted into each of the tubes containing the brush. The sample tubes were capped and vortexed for (10-15) seconds and then incubated at room temperature for 20 minutes. Each sample takes four (4) PCR microtubes labelled with the four different primers PM-1, PM-2, PM-3 and PM-4. 23ul of the master mix is pipetted into the respective labelled PCR tube. 2ul of the sample was then measured with the aid of a pipette into the PCR tubes with the master mix respectively. Also, 2ul each of the NC templates was pipetted into the PCR microtubes labelled NC and 2ul of the positive template was added to the PCR tubes labelled PC. PCR tubes were

gently vortexed to ensure the mixture was uniformly mixed. Using a refrigerated centrifuge, tubes with sample mixture were span to bring the liquid to the bottom of the wells. All the PCR tubes were capped tightly and placed into the wells in the Atilla Biosystems' Ampfire system, a real-time PCR machine. The lid of the thermal cycler was closed and the reaction run started. A Bio-Rad CFX-96 real-time PCR system was used to incubate the experiment tubes for 75 minutes at 60 °C while monitoring the fluorescence from the FAM/HEX/ROX/CY5 channels once per minute. Samples were completely run in 1hr45min. Genotyping findings were coded and recognized based on exponential amplification curves in the *CY5*, *ROX*, *FAM*, and *HEX* channels**.** Each primer detected the following hr-HPV types: Primer 1 (PM-1): hr-HPV31, 51, 39 and 16. Primer 2 (PM-2): hr-HPV35, 68, 18 and 59. Primer 3 (PM-3): hr-HPV33, 66 and 45. Primer 4 (PM-4): hr-HPV58, 56, 53 and 52.

Data entry and analysis

Data generated from the laboratory tests described were entered into a Microsoft Excel sheet. Consistency checks were applied to ensure the right and logical flow of data was entered. Outliers were consistently checked before data was presented in summary tables and exported to Stata v.16 for statistical analyses. The data was stratified into two categories, the socio-demographic characteristics and the prevalence rates of HPV and cervical cancer percentages.

Continuous data were described in terms of mean with standard deviations, and medians with inter-quartile ranges while categorical data were displayed as proportions. Continuous data were compared to each other using an independent t-test. Categorical data on the other hand were compared using

chi-square analysis. Bivariate and multivariate linear regression models were then employed to assess the scores obtained from the study participants. Baseline variables were controlled in the regression models and intra-class correlation co-efficient was assessed for clustering effect. All statistical tests were considered statistically significant at $p<0.05$.

Chapter Summary

This section presents a comprehensive overview of the research methodology implemented in a cross-sectional study based in a hospital, examining hr-HPV screening in Women Living with HIV (WLHIV) at the Cape Coast Teaching Hospital (CCTH) in Ghana. The chapter includes details on the study design, location, sample collection, processing protocols, molecular assays utilized for hr-HPV DNA detection, as well as the statistical tools employed for data analysis.

CHAPTER FOUR

RESULTS AND DISCUSSION

Introduction

This chapter presents the results obtained from the study and discusses the study findings. The socio-demographics and behavioral characteristics of the study population such as age, age at first sex, number of sexual partners, contraceptive use, number of pregnancies, marital status, history of smoking etc are well illustrated. The chapter also presents the knowledge level of study participants n HPV and CC and the distribution of hr-HPV among WLHIV. The association between multiple hr-HPV co-infection, HPV 16/18 infection and behavioral characteristics of the study participants are well expounded by using logistic regression analysis.

Results

Sociodemographic and behavioral characteristics

Table 1 depicts the sociodemographic features of 330 study participants. The mean age of the study participants was 47.2 years (SD ±10.7) and mean age at first sex was 18.7 years (SD±3.3). Approximately 49.7% of the participants had secondary education. The median number of pregnancies was 4 (Inter quartile range [IQR], 2-5) and most of the women (53.3%) had1 to 3 children. Among women who had been sexually active in the last three months (N=172), the rate of consistent condom usage was (77.9%). Most women (48.5%) were on ART for one to less than five months and 56.6% of the women had their HIV viral loads less than 1000copies/ml.

Table 1: Socio-demographic, behavioral and clinical characteristics of study participants (N=330)

Variables	Number (n)	Percentage (%) SD OR IQR
Age (years)		
Mean	47.2	10.7
25-34	40	12.1
35-44	95	28.8
45-54	107	32.4
≥ 55	88	26.7
Educational level		
No formal education/Primary	137	41.5
JHS/Secondary	164	49.7
Tertiary	29	8.8
Marital status		
Single	75	22.7
Married/Cohabiting	124	37.6
Widowed/Divorced	131	39.7
Occupation		
Unemployed	68	20.6
Unskilled work	191	57.9
Skilled work	71	21.5
Religion		
Christianity	296	89.7
Islam	34	10.3
Number of pregnancies		
Median	4	2-5
0	19	5.76
1-3	135	40.91
4-6	134	40.60
≥7	42	12.72
Number of children		
Median	3	2-4
0	35	10.7
1-3	176	53.3
4-6	105	31.8
≥7	14	4.2
Number of Lifetime Sexual partners		
Median	3	2-3
1-2	157	47.9
3-6	168	51.2
≥7	3	0.9
Age at first sex (326)		
Mean, SD	18.7	3.3
≤16	95	28.1

17-25	221	67.8
≥26	10	3.03
Currently sexually active (last 3 months)		
Yes	182	55.2
No	148	44.8
Condom use in the last 3 months (N=172)		
Yes	134	77.9
No	38	22.1
Ever used hormonal contraceptives		
Yes	129	39.1
No	201	60.9
Current hormonal contraceptive use		
Yes	53	16.1
No	277	83.9
Menarche (years) (N=325)		
Mean	15.3	2.0
≤13	47	14.5
14-19	267	82.2
≥20	11	3.3
Still menstruates		
Yes	153	46.4
No	177	53.6
Currently smokes cigarettes		
Yes	6	1.8
No	324	98.2
Duration of HIV Diagnosis (years)		
Median, IQR	4.0	1.3-8.0
< 1	40	12.1
1-<5	142	43.0
5-10	98	29.7
>10	50	15.2
Duration on ART (years)		
Median	46	15-80
< 1	52	15.8
1-<5	160	48.5
5-10	75	22.7
>10	43	13.0
Viral Load (copies/ml) (N=272)		
Median	411.5	36-1588
Target Not Detected	34	12.5
<20	0	0.0
20-999	154	56.6
≥1000	84	30.9

Source: Data obtained from Student's field work, 2021

Study participants' knowledge of HPV and cervical cancer

Table 2 depicts the knowledge of HPV and CC of 330 study participants. Of the number of women (80) who had heard of HPV, only 26.25% believed men could be infected with HPV, 80% of them believed HPV is the cause of cervical cancer, and 58.75% had heard of HPV. Also, 88% of study participants responded that HPV was transmitted via sexual intercourse as against 5.33% who believed transmission was through respiratory droplets and orofecal. Furthermore, 89.4% of the women believed CC was rare in Ghana, with 80% of the women with the view that CC was not preventable. Majority of the study participants (58.8%) had heard of CC screening whereas 41.2% had not.

Table 2: Knowledge of study population on HPV and cervical cancer (N=330)

Variables	Number (n)	Percentage (%)
Heard of HPV before?		
Yes	80	24.2
No	250	75.8
Men can be infected with HPV (N= 80)		
Yes	21	26.25
No	24	30.00
Don't know	35	43.75
How is HPV transmitted? (N= 75)		
Oro-faecal	4	5.33
Respiratory droplets	4	5.33
Sexual intercourse	66	88.00
Oro-faecal/ Respiratory droplets	1	1.33
HPV causes Cervical cancer		
Yes	64	80.00
No	1	1.25
I don't know	15	18.75
Heard of HPV Vaccine		
Yes	47	58.75
No	33	41.25
Is HPV vaccine accessible in Ghana? (47)		
Yes	42	89.4
No	0	0.00
Don't know	5	10.6
Cervical cancer is rare in Ghana (N=330)		
Yes	57	17.3
No	273	82.7
Family history of cervical cancer is a risk factor		
Yes	39	11.8
No	291	88.2
Usage of herbal vagina preparation increases chances of cervical cancer		
Yes	80	24.2
No	250	75.8
History of abortion or miscarriages is a risk factor for cervical cancer		
Yes	63	19.1
No	267	80.9
Which of these is a sign of cervical cancer?	Yes	No
	n (%)	n (%)
Bleeding after sex	121 (36.7)	209 (63.3)
Offensive vaginal discharge	132 (40.0)	198 (60.0)
Itchy vagina	70 (21.2)	260 (78.8)

Bleeding in-between menstruation	116 (35.2)	214 (64.8)
No symptoms	108 (32.7)	222 (67.3)
Cervical cancer is always fatal		
Yes	66	20.0
No	264	80.0
Cervical cancer is preventable		
Yes	247	74.8
No	83	25.2
Heard of Cervical Cancer Screening before?		
Yes	136	41.2
No	194	58.8
Type(s) of Cervical Cancer screening you know (N= 132)		
PAP smear	34	25.8
VIA	56	42.4
HPV test	1	0.7
PAP/VIA	36	27.3
PAP/VIA/HPV test	5	3.8
It's easy to have cervical screening in Ghana		
Yes	53	39.3
No	60	44.4
Don't know	22	16.3
Only women with vaginal complaints should have cervical screening		
Yes	94	28.5
No	236	71.5
Have you screened for cervical cancer before?		
Yes	50	37.0
No	85	63.0
Reasons for cervical cancer (N= 50)		
Free screening was available	30	60.0
It was requested for me in the hospital	11	22.0
I went to ask for it myself and paid	9	18.0

Source: Source: Data obtained from Student's field work, 2021.

Study participants' knowledge of cervical cancer

Table 3 displays the relationship between participants' cervical cancer knowledge and their sociodemographic and behavioral characteristics. The ages of participants ($p<0.001$), educational level ($p<0.001$) and marital status ($p=0.009$) were significantly related to participants' knowledge of cervical

cancer. In addition, the number of pregnancies ever had by the women (p=0.038) and women who were currently sexually active (p=0.008) were associated with cervical cancer knowledge. Furthermore, current use of hormonal contraceptives (p=0.051), menstrual status (p<0.001) and cervical cancer screening awareness (p<0.001) showed significant association with cervical cancer knowledge of the study participants.

Table 3: Association between knowledge of cervical cancer and sociodemographic and behavioral characteristics (N=330).

Variable	Insufficient knowledge	Sufficient knowledge	p-value
	n (%)	n (%)	
Age			***<0.001***
25-34	13 (32.5)	27 (67.5)	
35-44	38 (40.0)	57 (60.0)	
45-54	55 (51.4)	52 (48.6)	
≥ 55	59 (67.1)	29 (32.9)	
Educational level			***<0.001***
No formal education/Primary	87 (63.5)	50 (36.5)	
JHS/Secondary	76 (46.3)	88 (53.7)	
Tertiary	2 (6.9)	27 (93.1)	
Marital status			***0.004***
Single	30 (40.0)	45 (60.0)	
Married/Cohabiting	55 (44.4)	69 (55.6)	
Widowed/Divorced	80 (61.1)	51 (38.9)	
Occupation			0.334
Unemployed	36 (52.9)	32 (47.1)	
Unskilled work	99 (51.8)	92 (48.2)	
Skilled work	30 (42.3)	41 (57.7)	
Religion			0.469
Christianity	146 (49.3)	150 (50.7)	
Islam	19 (55.9)	15 (44.1)	
Number of pregnancies ever had			***0.022***
0	5 (26.3)	14 (73.7)	
1-3	63 (46.7)	72 (53.3)	
4-6	69 (51.5)	65 (48.5)	
≥ 7	28 (66.7)	14 (33.3)	
Number of sexual partners ever had			1.00
1-2	79 (50.3)	78 (49.7)	
3-6	84 (50.0)	84 (50.0)	
≥ 7	1 (33.3)	2 (66.7)	
Age at first sex			0.735
≤ 16	51 (53.7)	44 (46.3)	
17-25	108 (48.9)	113 (51.1)	
≥ 26	5 (50.0)	5 (50.0)	
Are you currently sexually active?			***0.008***
Yes	79 (43.4)	103 (56.6)	

No	86 (58.1)	62 (41.9)	
Use condom regularly during sex?			0.235
Yes	56 (41.8)	78 (58.2)	
No	20 (52.6)	18 (47.4)	
Ever used any hormonal contraceptive			0.735
Yes	63 (48.8)	66 (51.2)	
No	102 (50.8)	99 (49.2)	
Do you currently use hormonal contraceptive?			***0.051***
Yes	20 (37.7)	33 (62.3)	
No	145 (52.3)	132 (47.7)	
Number of children			***0.014***
0	14 (40.0)	21 (60.0)	
1-3	79 (44.9)	97 (55.1)	
4-6	61 (58.1)	44 (41.9)	
≥ 7	11 (7.0)	3 (21.4)	
Menarche			0.602
≤ 13	22 (46.8)	25 (53.2)	
14-19	135 (50.6)	132 (49.4)	
≥ 20	4 (36.4)	7 (63.6)	
Are you still menstruating?			***<0.001***
Yes	53 (34.6)	100 (65.4)	
No	112 (63.3)	65 (36.7)	
Do you currently smoke?			0.214
Yes	1 (16.7)	5 (83.3)	
No	164 (50.6)	160 (49.4)	
Duration on ART			0.495
< 1	23 (44.2)	29 (55.8)	
1-4	77 (48.1)	83 (51.9)	
5-10	40 (53.3)	35 (46.7)	
≥ 11	25 (58.1)	18 (41.9)	
Viral load			0.763
<1000	80 (51.9)	74 (48.1)	
> 1000	40 (47.6)	44 (52.4)	
Have you ever heard of HPV?			***<0.001***
Yes	13 (16.3)	67 (83.7)	
No	152 (60.8)	98 (39.2)	
Heard of cervical cancer screening?			***<0.001***
Yes	30 (63.0)	106 (68.0)	
No	135 (69.6)	59 (97.0)	
Easy to have cervical cancer screening in Ghana (N=135)			0.488
Yes	9 (17.0)	44 (83.0)	
No	15 (25.0)	45 (75.0)	
Don't know	6 (27.3)	16 (72.7)	
Have you ever had cervical cancer screening? (N=135)			0.634
Yes	10 (20.0)	40 (80.0)	
No	20 (23.5)	65 (76.5)	

Source: Data obtained from student's field work, 2021

Factors associated with study participants' knowledge about cervical cancer

Table 4 summarizes the bivariate and multivariate logistic regressions with women's knowledge about cervical cancer (insufficient or sufficient knowledge) as the main outcome. In the multivariate model, the educational level of the women was the only significant variable (likelihood ratio $p<0.001$). Women with tertiary education were 7.55 times more likely to have sufficient knowledge on cervical cancer as compared to those without formal/primary education (AOR=7.55, 95% CI: 1.34-42.43, p=0.022). Participants' menstrual status (AOR=0.22, 95% CI: 0.09-0.54, p=0.001), having heard of HPV (AOR=0.24, 95% CI: 0.11-0.51, $p<0.001$) and awareness of CC screening (AOR=0.10, 95% CI: 0.05-0.19, $p<0.001$) had less likelihood of having sufficient CC knowledge. Even with p-values less than 0.001, these variables did not significantly relate to cervical cancer awareness (likelihood ratio p=0.241) in the multivariate model.

Table 4: Predictors of the level of cervical cancer knowledge

Variable	OR (95% CI)	p-value	AOR (95% CI)	p-value
Age				
25-34	1		1	
35-44	0.72 (0.33-1.57)	0.413	0.91 (0.31-2.72)	0.871
45-54	0.46 (0.21-0.98)	0.043	1.02 (0.29-3.55)	0.981
≥ 55	0.24 (0.11-0.53)	<0.001	0.39 (0.08-1.79)	0.225
Educational level*				
No education /Primary	1		1	
JHS/Secondary	0.40 (0.19-0.83)	0.014	1.82 (0.99-3.32)	***0.052***
Tertiary	1.14 (0.64-2.02)	0.652	7.55 (1.34-42.43)	***0.022***
Marital status				
Single	1		1	
Married/Cohabiting	0.84 (0.47-1.50)	0.547	0.61 (0.31-1.48)	0.333
Widowed/Divorced	0.43 (0.24-0.76)	0.004	0.49 (0.21-1.12)	0.090
Number of pregnancies ever had				
0	1		1	
1-3	0.41 (0.14-1.20)	0.103	0.34 (0.05-2.30)	0.267
4-6	0.34 (0.11-0.99)	0.047	0.34 (0.04-2.67)	0.305
≥ 7	0.18 (0.05-0.60)	0.005	0.24 (0.03-2.36)	0.223
Are you currently sexually active?				
Yes	1		1	
No	0.55 (0.36-0.86)	0.008	1.99 (0.92-4.32)	0.081
Heard of HPV? **				
Yes	1		1	
No	0.13 (0.07-0.24)	<0.001	0.24 (0.11-0.51)	***<0.001***
Are you still menstruating? **				
Yes	1		1	
No	0.71 (0.19-0.48)	<0.001	0.22 (0.09-0.54)	***0.001***
Number of children				
0	1		1	
1-3	0.82 (0.39-1.71)	0.595	3.52 (0.74-16.73)	0.113
4-6	0.48 (0.22-1.04)	0.066	5.16 (0.84-31.67)	0.076
≥ 7	0.18 (0.04-0.77)	0.021	1.88 (0.13-27.62)	0.645
Heard of cervical cancer screening? **				
Yes	1		1	
No	0.12 (0.07-0.21)	<0.001	0.10 (0.05-0.19)	***<0.001***

*Likelihood ratio p-value<0.001 **Likelihood ratio p-value=0.241
OR = Odds ratio AOR = Adjusted odds ratio CI = Confidence interval

Source: Data obtained from student's field work, 2021.

Prevalence of hr-HPV and HPV genotypes distribution among study participants

The distribution of HPV genotypes among 141 HIV/HPV co-infected women is presented in **Table 5**. Hr-HPV was detected in 42.7% (95% C.I: 37.4-48.1) of the study population (**Fig. 3**). The top five most prevalent hr-HPV types were HPV59 (50.4%), HPV18 (30.5%), HPV35 (26.2%), HPV58 (17%) and HPV45 (14.9%) **(Table 5).** In total, 60.3% of HIV/HPV co-infected women had multiple hr-HPV infections. About 44% of women with multiple hr-HPV were found to have been infected with 2 to5 hr-HPV types whilst 19.9% had been infected by more than five hr-HPV types. About 37.6% of WLHIV had HPV16/18.

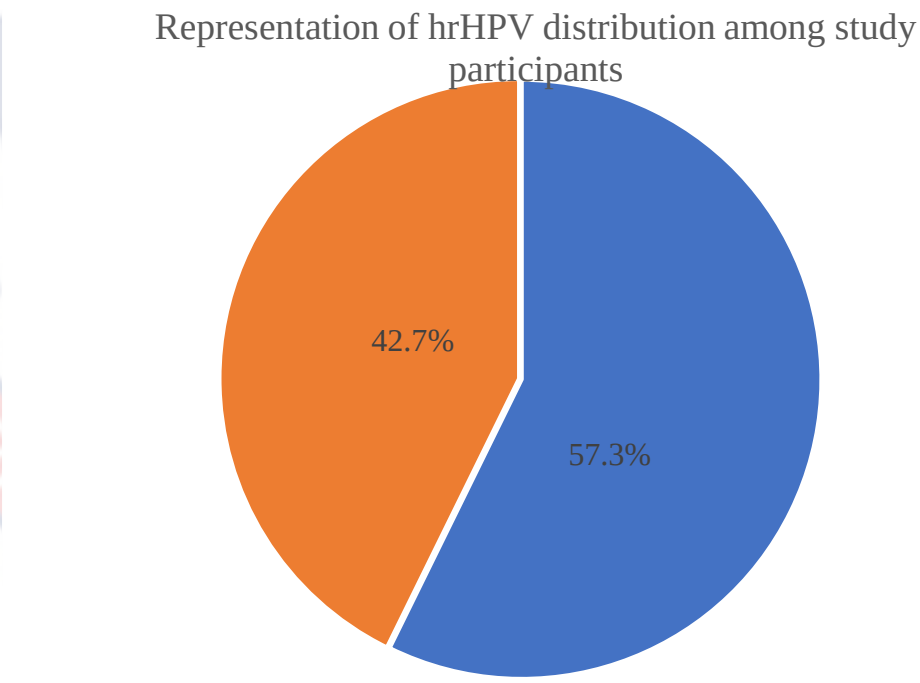

Figure 3: The distribution of hr-HPV prevalence among study participants (N=330).

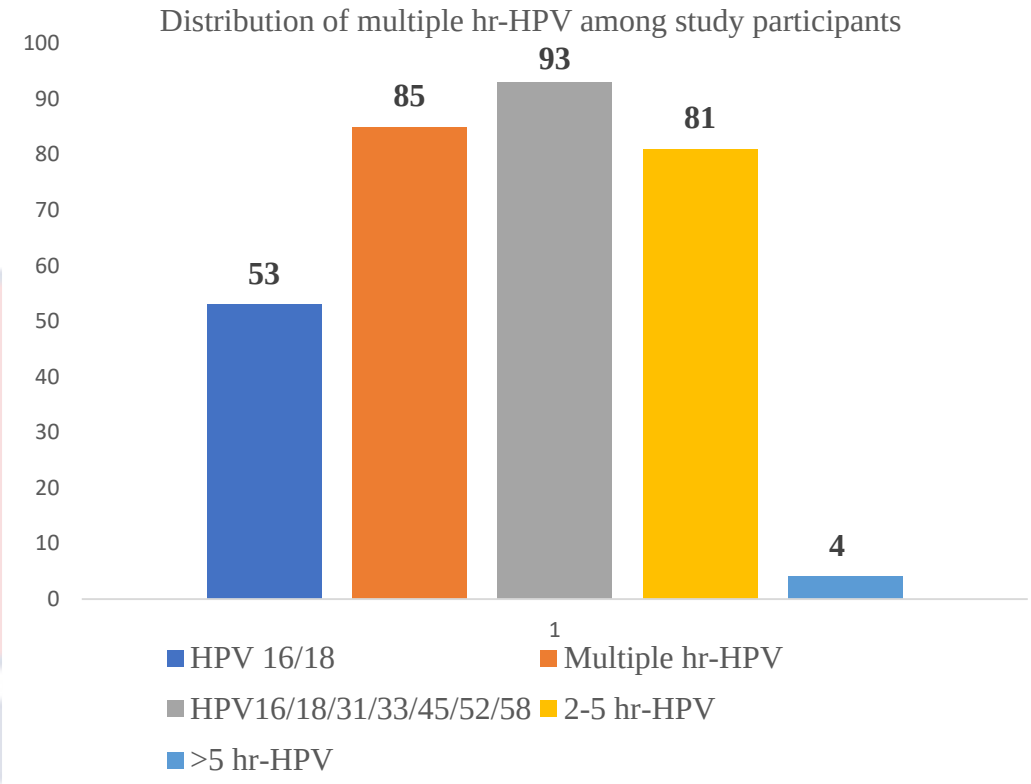

Figure 4: The distribution of Multiple hr-HPV among study participants.

Table 5: HPV prevalence and distribution of HPV genotypes among HIV/HPV co-infected women (N=141)

Type of HPV genotype	Number of HPV	Percentage (%)
HPV16	13	9.22
HPV18	43	30.50
HPV31	16	11.35
HPV33	4	2.84
HPV35	37	26.24
HPV39	10	7.10
HPV45	21	14.89
HPV51	9	6.38
HPV52	20	14.18
HPV53	19	13.48
HPV56	12	8.51
HPV58	24	17.02
HPV59	71	50.35
HPV66	13	9.22
HPV68	17	12.06

Source: Data obtained from Student's laboratory work, 2021

HIV/HPV co-infection among study participants

Table 6 summarizes the relationship between HIV/HPV co-infection and study participants' sociodemographic and behavioral characteristics. Aside duration of ART ($p=0.047$) and viral load ($p<0.001$) that showed significant relation with HIV/HPV co-infection, all other variables presented no association with HIV/HPV co-infection among the women.

Table 6: Association between HIV/HPV coinfection and the socio-demographic and behavioral characteristics (N=330).

Variable	HIV/HPV Co-infection		p-value
	No	Yes	
	n (%)	n (%)	
Age			0.362
25-34	20 (50.0)	20 (50.0)	
35-44	52 (54.7)	43 (45.3)	
45-54	60 (56.1)	47 (43.9)	
≥ 55	57 (64.8)	31 (35.2)	
Age at first sex			0.189
<=16	57(60.0)	38(40.0)	
17-25	127(57.5)	94(42.5)	
>=26	3(30.0)	7(70.0)	
Educational level			0.930
No formal education/Primary	80 (58.4)	57 (41.6)	
JHS/Secondary	93 (56.7)	71 (43.3)	
Tertiary	16 (55.2)	13 (44.8)	
Marital status			0.092
Single	36 (48.0)	39 (52.0)	
Married/Cohabiting	79 (63.7)	45 (36.3)	
Widowed/Divorced	74 (56.5)	57 (43.5)	
Occupation			0.147
Unemployed	34 (50.0)	34 (50.0)	
Trader/Unskilled work	118 (61.8)	73 (38.2)	
Civil servant/clerical/Professional	37 (52.1)	34 (47.9)	
Religion			0.355
Christianity	167 (56.4)	129 (43.6)	
Islam	22 (64.7)	12 (35.3)	
Number of pregnancies ever had			0.566
0	10 (52.6)	9 (47.4)	
1-3	73 (54.1)	62 (45.9)	
4-6	83 (61.9)	51 (38.1)	
≥ 7	23 (54.8)	19 (45.2)	
Number of sexual partners ever had			0.532
1-2	85 (54.1)	72 (45.9)	
3-6	101 (60.1)	67 (39.9)	
≥ 7	2 (66.7)	1 (33.3)	
Age at first sex			0.189
≤ 16	57 (60.0)	38 (40.0)	
17-25	127 (57.5)	94 (42.5)	
≥ 26	3 (30.0)	7 (70.0)	
Are you currently sexually active?			0.958
Yes	104 (57.1)	78 (42.9)	
No	85 (57.4)	63 (42.6)	
Use condom regularly during sex?			0.566
Yes	81 (60.5)	53 (39.6)	

No	21 (55.3)	17 (44.7)	
Ever used any hormonal contraceptive			0.511
Yes	71 (55.0)	58 (45.0)	
No	118 (58.7)	83 (41.3)	
Do you currently use hormonal contraceptive?			0.309
Yes	27 (50.9)	26 (49.0)	
No	162 (58.5)	115 (41.5)	
Number of children			0.474
0	22 (62.9)	13 (37.1)	
1-3	95 (54.0)	81 (46.0)	
4-6	62 (59.0)	43 (41.0)	
≥ 7	10 (71.4)	4 (28.6)	
Menarche			0.230
≤ 13	28 (59.6)	19 (40.4)	
14-19	150 (56.2)	117 (43.8)	
≥ 20	9 (81.8)	2 (18.2)	
Are you still menstruating?			0.302
Yes	83 (54.3)	70 (45.8)	
No	106 (59.9)	71 (40.1)	
Do you currently smoke?			0.244
Yes	5 (83.3)	1 (16.7)	
No	184 (56.8)	140 (43.2)	
Duration on ART			***0.047***
< 1	28 (53.9)	24 (46.2)	
1-4	103 (64.4)	57 (35.6)	
5-10	34 (45.3)	41 (54.7)	
≥ 11	24 (55.8)	19 (44.2)	
Duration of HIV diagnosis (years)			0.112
< 1	21 (52.5)	19 (47.5)	
1-<5	92 (64.8)	50 (35.2)	
5-10	49 (50.0)	49 (50.0)	
>10	27 (54.0)	23 (46.0)	
Viral load (272)			***<0.001***
<1000	118 (62.8)	70 (37.2)	
≥ 1000	22 (26.2)	62 (73.8)	
Have you ever heard of HPV?			0.832
Yes	45 (56.3)	35 (43.8)	
No	144 (57.6)	106 (42.4)	
Heard of cervical cancer screening?			0.067
Yes	86 (63.2)	50 (36.8)	
No	103 (53.1)	91 (46.9)	
What type of cervical screening do you know?			0.813
PAP smear	23(67.7)	11(32.3)	
PAP smear/VIA	23(63.9)	13(36.1)	
PAP smear/VIA/HPV test	4(80.0)	1(20.0)	
VIA	34(60.71)	22(39.3)	

HPV test	1(100)	0(0.00)	
Easy to have cervical cancer screening in Ghana (135)			0.131
Yes	37 (69.8)	16 (30.2)	
No	39 (65.0)	21 (35.0)	
Don't know	10 (45.5)	12 (54.6)	
Have you ever had cervical cancer screening? (135)			0.426
Yes	34 (68.0)	16 (32.0)	
No	52 (61.2)	33 (38.8)	
How long has it been since you were diagnosed with HIV?			0.112
<1	21(52.5)	19(47.5)	
1-5	92(64.8)	50(35.2)	
5-10	49(50.0)	49(50.0)	
>10	27(57.3)	23(46.0)	
Knowledge about cervical cancer			0.095
Insufficient knowledge	102 (61.8)	63 (38.2)	
Sufficient knowledge	87 (52.7)	78 (47.3)	

Source: Data obtained from Student's field work, 2021

Predictors of HIV/HPV co-infection

Both bivariate and multivariable regressions with HIV/HPV co-infection status as the main dependent variable are presented in Table 7 below. In the multivariable regression, the odds of women who had never heard of cervical cancer screening had a 2.8 times higher chance of having both HIV and HPV co-infection than those who had heard of CC screening. (AOR=2.80, 95% CI: 1.46-5.35, p=0.002). In addition, women with knowledge about CC (AOR=2.29, 95% CI: 1.20-4.37, p=0.002) and women with high viral load (AOR=5.58, 95% CI: 2.89-10.78, p<0.001) were respectively 2.29 and 5.58 times more likely to be HIV/HPV co-infected. Although women of ages ≥55 years (AOR=0.23 95% CI: 0.07-0.71, p=0.011) showed less likelihood of co-infection compared with women within the age 25 to34, the overall age variable was not significant (p=0.056) in the multivariate model.

Table 7: Predictors of HIV/HPV co-infection

Variable	OR (95% CI)	p-value	AOR (95% CI)	p-value
Age*				
25-34	1		1	
35-44	0.83 (0.39-1.73)	0.615	0.43 (0.16-1.16)	0.096
45-54	0.78 (0.38-1.62)	0.511	0.50 (0.18-1.34)	0.168
≥ 55	0.54 (0.25-1.16)	0.116	0.23 (0.07-0.71)	***0.011***
Marital status				
Single	1		1	
Married/Cohabiting	0.53 (0.29-0.94)	0.031	0.67 (0.32-1.39)	0.278
Widowed/Divorced	0.71 (0.40-1.26)	0.241	1.14 (0.52-2.48)	0.739
Heard of cervical cancer screening?				
Yes	1		1	
No	1.52 (0.97-2.38)	0.067	2.80 (1.46-5.35)	***0.002***
Knowledge about cervical cancer				
Insufficient knowledge	1		1	
Sufficient knowledge	1.45 (0.94-2.25)	0.096	2.29 (1.20-4.37)	***0.012***
Duration on ART				
<1	1		1	
1-4	0.65 (0.34-1.22)	0.176	0.32 (0.08-1.30)	0.112
5-10	1.41 (0.69-2.86)	0.346	0.68 (0.16-2.90)	0.600
≥11	0.92 (0.41-2.08)	0.848	0.50 (0.11-2.29)	0.111
Viral load				
<1000	1		1	
≥1000	4.75 (2.69-8.39)	<0.001	5.58 (2.89-10.78)	<0.001

*Likelihood ratio p-value for age = 0.056

Source: Data obtained from Student's field work, 2021

Status of HPV 16/18 among study participants

It was found that there was a significant association between HPV 16/18 genotype status and the number of pregnancies among study participants (p=0.029) with majority of the women (40.3%) recording one to three pregnancies followed by women who reported four to six pregnancies (33.3%) (**Table 8**). Also, there was an association between HPV 16/18 and the women's knowledge of cervical cancer screening accessibility in Ghana

(p=0.009). All other variables showed no significant association with HPV 16 and/or 18

Table 8: Association between HPV 16and/or 18 and the behavioral characteristics of the study population (N=141).

Variable	HPV 16 and/ 18 No	Yes	p-value
	n (%)	n (%)	
Age			0.061
25-34	14 (70.0)	6 (30.0)	
35-44	24 (55.8)	19 (44.2)	
45-54	2 5(53.2)	22 (46.8)	
≥ 55	25 (80.7)	6 (19.3)	
Age at first sex			0.289
≤ 16	27 (71.0)	11(29.0)	
17-25	57 (60.6)	37 (39.4)	
≥ 26	3 (42.9)	4 (57.1)	
Educational level			0.134
No formal education/Primary	35 (61.4)	22 (38.6)	
JHS/Secondary	48 (67.6)	23 (32.4)	
Tertiary	5 (38.5)	8 (61.5)	
Marital status			0.423
Single	21 (53.9)	18 (46.1)	
Married/Cohabiting	30 (66.7)	15 (33.3)	
Widowed/Divorced	37 (64.9)	20 (35.1)	
Occupation			0.615
Unemployed	19 (55.9)	15 (44.1)	
Trader/Unskilled work	48 (65.8)	25 (34.2)	
Civil servant/clerical/Professional	21 (61.8)	13 (38.2)	
Religion			
Christianity	79 (61.2)	50 (38.8)	
Islam	9 (75.0)	3 (25.0)	
Number of pregnancies ever had			***0.029***
0	2 (22.2)	7 (77.8)	
1-3	37 (59.7)	25 (40.3)	
4-6	34 (66.7)	17 (33.3)	
≥ 7	15 (79.0)	4 (21.0)	
Number of sexual partners			0.929
1-2	45 (62.5)	27 (37.5)	
3+	42 (61.8)	26 (38.2)	
Are you currently sexually active?			
Yes			
No	25 (39.7)	38 (60.3)	
Use condom regularly during sex?			0.981
Yes	22 (41.5)	31 (58.5)	
No	7 (41.2)	10 (58.8)	
Ever used any hormonal contraceptive?			0.179
Yes	40 (69.0)	18 (31.0)	

No	48 (57.8)	35 (42.2)	
Do you currently use hormonal contraceptive?			0.919
Yes	16 (61.5)	10 (38.5)	
No	72 (62.6)	43 (37.4)	
Number of children			0.284
0	6 (46.1)	7 (53.9)	
1-3	48 (59.3)	33 (40.7)	
4-6	31 (72.1)	12 (27.9)	
7+	3 (75.0)	1 (25.0)	
Menarche			0.592
≤ 13	10 (52.6)	9 (47.4)	
14-19	75 (64.1)	42 (35.9)	
≥ 20	1 (50.0)	1 (50.0)	
Are you still menstruating?			0.103
Yes	39 (55.7)	31 (44.3)	
No	49 (69.0)	22 (31.0)	
Do you currently smoke?			
Yes	0 (0.0)	1 (100)	
No	88 (62.4)	53 (37.6)	
How long has it been since you were diagnosed with HIV?			0.539
< 1	14 (73.7)	5 (26.3)	
1-5	29 (58.0)	21 (42.0)	
5-10	29 (59.2)	20 (40.8)	
> 10	16 (69.6)	7 (30.4)	
Duration on ART			0.102
< 1	18 (75.0)	6 (25.0)	
1-4	34 (59.6)	23 (40.4)	
5-10	21 (51.2)	20 (48.8)	
≥ 11	15 (79.0)	4 (21.0)	
Viral load (copies/ml)			0.372
< 1000	41 (66.1)	29 (41.4)	
≥ 1000	41 (62.1)	21 (33.9)	
Patient's Knowledge of multiple hr-HPV coinfection			0.348
Insufficient knowledge	42 (66.7)	21 (33.3)	
Sufficient knowledge	46 (59.0)	32 (41.0)	

Source: Data obtained from Student's field work, 2021

Factors associated with HPV 16 and/or 18

In the multivariable regression, association of the number of pregnancies and HPV 16 and/or 18 was statistically significant (likelihood ratio p-value=0.049). Also, the odds of having one to three pregnancies, , four to six and seven or more pregnancies were respectively 91%, 93% and 95%

less likely to have HV 16/18 genotype as compared to those who had had no pregnancy.

Table 9: Predictors of HPV 16 and/or 18

Variable	OR (95% CI	P-value	AOR (95% CI)	P-value
Age				
25-34	1		1	
35-44	1.85 (0.60-5.72)	0.287	3.00 (0.80-11.18)	0.103
45-54	2.05 (0.67-6.26)	0.206	2.65 (0.69-10.27)	0.158
55+	0.56 (0.15-2.07)	0.385	0.90 (0.17-4.74)	0.896
Number of pregnancies *				
0	1		1	
1-3	0.19 (0.04-1.01)	0.051	0.09 (0.01-0.92)	***0.043***
4-6	0.14 (0.03-0.76)	0.023	0.07 (0.01-0.73)	***0.026***
≥ 7	0.08 (0.01-0.52)	0.009	0.05 (0.00-0.65)	***0.022***
Viral load (copies/ml)				
< 1000	1		1	
≥ 1000	0.72 (0.36-1.47)	0.372	0.85 (0.38-1.88)	0.683

OR= Odds ratio AOR=Adjusted odds ratio CI= confidence interval
*Likelihood ratio p-value for number of pregnancies = 0.049.
Source: Data obtained from Student's field work, 2021

Multiple hr-HPV co-infection among study participants

Table 10 presents the association between multiple hr-HPV co-infection and participants' sociodemographic and behavioral characteristics. Multiple hr-HPV co-infections did not significantly correlate with any of the independent factors.

Table 10: Association between multiple hr-HPV co-infection and sociodemographic and behavioral characteristics of study participants (141)

Variable	Multiple Hr-HPV Co-infection		p-value
	No	Yes	
	n (%)	n (%)	
Age (years)			0.388
25-34	10 (50.0)	10 (50.0)	
35-44	14 (32.6)	29 (67.4)	
45-54	17 (36.2)	30 (63.8)	
≥ 55	15 (48.4)	16 (51.6)	
Age at first sex (years)			0.365
≤ 16	15 (39.5)	23 (60.5)	
17-25	39 (41.5)	55 (58.5)	
≥ 26	1 (14.3)	6 (85.7)	
Educational level			0.751
No formal education/Primary	24 (42.1)	33 (57.9)	
JHS/Secondary	28 (39.4)	43 (60.6)	
Tertiary	4 (30.8)	9 (69.2)	
Marital status			0.632
Single	13 (33.3)	26 (66.7)	
Married/Cohabiting	19 (42.2)	26 (57.8)	
Widowed/Divorced	24 (42.1)	33 (57.9)	
Occupation			0.970
Unemployed	13 (38.2)	21 (61.8)	
Trader/Unskilled work	29 (39.7)	44 (60.3)	
Civil servant/clerical/Professional	14 (41.2)	20 (58.2)	
Religion			0.276
Christianity	53 (41.1)	76 (58.9)	
Islam	3 (25.0)	9 (75.0)	
Number of pregnancies ever had			0.207
0	1 (11.1)	8 (88.9)	
1-3	29 (46.8)	33 (53.2)	
4-6	19 (37.3)	32 (62.7)	
≥ 7	7 (36.8)	12 (63.2)	
Number of sexual partners			0.918
1-2	30 (41.7)	42 (58.3)	
3-6	26 (38.8)	41 (61.2)	
7+	0 (0.0)	1 (100)	
Are you currently sexually active?			0.994
Yes	31 (39.7)	47 (60.3)	
No	25 (39.7)	38 (60.3)	
Use condom regularly during sex?			0.981
Yes	22 (41.5)	31 (58.5)	
No	7 (41.2)	10 (58.8)	
Ever used any hormonal contraceptive?			0.736

Yes	24 (41.4)	34 (58.6)	
No	32 (38.6)	51 (61.4)	
Do you currently use hormonal contraceptive?			0.765
Yes	11 (42.3)	15 (57.7)	
No	45 (39.1)	70 (60.9)	
Number of children			0.323
0	4 (30.8)	9 (69.2)	
1-3	35 (43.2)	46 (56.8)	
4-6	17 (39.5)	26 (60.5)	
7+	0 (0.0)	4 (100)	
Menarche			0.932
≤ 13	8 (42.1)	11 (57.9)	
14-19	46 (39.3)	71 (60.7)	
≥ 20	1 (50.0)	1 (50.0)	
Are you still menstruating?			0.535
Yes	26 (37.1)	44 (62.9)	
No	30 (42.2)	41 (57.8)	
Do you currently smoke?			
Yes	0 (0.0)	1 (100)	
No	56 (40.0)	84 (60.0)	
How long has it been since you were diagnosed with HIV?			0.947
<1	8 (42.1)	11 (57.9)	
1-5	20 (40.0)	30 (60.0)	
5-10	18 (36.7)	31 (63.3)	
>10	10 (43.5)	13 (56.5)	
Duration on ART			0.311
<1	11 (45.8)	13 (54.2)	
1-4	23 (40.3)	34 (59.7)	
5-10	12 (29.3)	29 (70.7)	
≥ 11	10 (52.6)	9 (47.4)	
Viral load (copies/ml)			0.350
< 1000	26 (37.1)	44 (62.9)	
≥ 1000	28 (45.2)	34 (54.8)	
Patients' Knowledge of multiple hr-HPV coinfection			0.735
Insufficient knowledge	26 (41.3)	37 (58.7)	
Sufficient knowledge	30 (38.5)	48 (61.5)	

Source: Data obtained from Student's field work, 2021

Discussion

This research determined the role of HPV DNA testing for CC screening among WLHIV at the CCTH.

Sociodemographic and behavioral characteristics

From responses gathered from the questionnaires, the mean age of the study participants was 47.2 years and more than one-third of the study participants were between the ages of 45-54. This was slightly above the mean ages 44 and 41 years obtained in studies by Obiri-Yeboah et al and Acheampong et al respectively (Acheampong et al., 2021; Obiri-Yeboah. et al., 2017). This implied that a significant part of WLHIV in the study were beyond the WHO-designated priority age bracket for screening, which is 25-45 years (WHO, 2021a). Again, most of the WLHIV recruited for this study were engaged in unskilled occupations as was the case in the study by Krings et al (Krings et al., 2019) and had low level of education. These sociodemographic factors as demonstrated in the multivariate analysis in this study have an impact on the knowledge and perception toward screening for CC (Adedimeji et al., 2021).

About 1.8% of WLHIV were found to be smokers and 18.8% use hormonal contraceptives respectively. This was similar to studies by Krings et al. and Obiri-Yeboah et al., who found 1% and 3.1% respectively of WLHIV to be smokers (Krings et al., 2019; Obiri-Yeboah, et al., 2017), hence, suggesting a decrease risk of HPV infection among the study participants. However, it is worth noting that the responses could be compromised by cultural norms in the Ghanaian society and hence, data on smoking and hormonal contraceptive use may be skewed. According to studies, having

numerous lifetime sexual partners increases the risk for HPV infection (Adams et al., 2019; Sellors et al., 2003). In this study, it was found that about 51.2% of women had three to six lifetime sexual partners and 55.1% had one to three children. In comparison with a study in Morocco by Belglania et al (Belglaiaa et al., 2015), this was high and increases women chances of been infected with hr-HPV. However, analysis from the study has indicated that there has been an improvement in condom use which suggest a further lower risk of HPV infection in the study populace.

Study participants' knowledge of HPV and cervical cancer

Multivariate logistic regression analysis showed that the knowledge of study participants on CC was significantly associated with level of education. Thus, having tertiary education made an individual seven times more likely to have had CC knowledge compared with a person with no education. This could be attributed to the individual's ability to search for information and/or make good use of the social media for information regarding CC. Also, women who were not menstruating, or who had not heard of HPV and CC screening were less likely to know about HPV and CC in this study, most of the study participants between 35-54 years demonstrated sufficient knowledge of CC. This may largely depend on individual experiences rather than community-based education on CC. The knowledge level of study population on HPV was low and significantly associated with risk of HPV and CC infection This was closely related to findings obtained from a study in South Africa and elsewhere in SSA that reported low knowledge level of HPV among study participants (Tiiti et al., 2022). These women may be more

susceptible to developing HPV infection due to their lack of awareness of the HPV virus

According to WHO report in 2019, knowledge and awareness of CC are inadequate in developing nations (WHO, 2019b). Ghana as a developing nation is no different as this study has shown out. The proportion of women who had heard of CC screening (41.2%) was lower compared with what has been reported by Gyamfua et al., in Ghana (55.5%) (Gyamfua et al., 2019) and Aswathy et al., in Kerala (72.1%) (Aswathy et al., 2012). This however indicated a higher risk of CC among WLHIV. Earlier investigations in Nigeria and South Africa among women seeking healthcare found that more than three-quarters of these women lacked knowledge of CC infection, indicating a lower level of knowledge than the current study (Okunade et al., 2017; Ramathuba and Ngambi, 2018). Study participants' knowledge of CC was statistically related to marital status (P=0.004) This could be attributed to the education they received from antennal/postnatal clinics and also from CC awareness programs organized by CCTH to women. A study in Bangladesh, focused on five questions about CC screening reported 8.3% of their research population had previously been screened (Islam et al., 2018). In contrast to our findings, a slightly higher percentage (37%) had screened for CC which confirms women inadequate knowledge of CC and HPV infection due to low level of formal education.

Hr-HPV and HPV genotypes distribution among study participants

Previous research has shown a rise in HPV prevalence, including hr-HPV, multiple HPV, and other HPV genotypes , in developed countries and across SSA (Ezechi et al., 2014). Obiri-Yeboah et al argued that HIV-1

seropositive women in Ghana as elsewhere were more often infected with HPV and more likely to have multiple HPV infections (Obiri-Yeboah. et al., 2017). In this study, the prevalence of hr-HPV genotypes obtained was 42.7% (**Fig 3**).

This was lower than what was obtained by Obiri-Yeboah et al., in a study conducted among 163 HIV seropositive women in Ghana (65.3%) (Obiri-Yeboah. et al., 2017). Nonetheless, this rate is higher than WHO's estimated prevalence of 21.3% used for West African countries among women between 30 to 49 years. Similarly, in a study among WLHIV/AIDS in Morocco, the prevalence of HPV infection was 74.5%, (Souho et al., 2016). This was high compared to the prevalence in our study population (42.7%). Religious, cultural practices in North Africa, inaccessibility of screening facilities and competent human resources.in this certain could be the major contributors to the high rate of hr-HPV recorded in the Moroccan study.

Notwithstanding, low prevalence of hr-HPV were reported in a few other studies in Ghana; 10.7% (Domfeh et al., 2008), 13.9% in south-west Ghana (Schulze et al., 2016) and 32.3% in North Tongu District (Krings et al., 2019). The difference in prevalence could be as a result of the difference in study targets or vulnerable group by each study and testing methods adapted.

The five most common individual hr.-HPV types in descending order of prevalence obtained in the study were HPV59(50.4%), HPV18(30.5%), HPV35(26.2%), HPV58(17%) and HPV45(14.9%) (**Table 5**). This is slightly similar to the findings of Ezechi *et al* in Nigeria (Ezechi et al., 2014). In a Ghanaian study by Yar *et al.*, (Yar et al., 2016) five main hr-HPV genotypes were 58, 35, 68, 31, and 18, whilst Brandful *et al.*, (Brandful et al., 2014)

found 68, 66, 58, 35, and 56. The most frequent HPV genotypes discovered in self-collected samples, according to Awua *et al.*, were HPV16 (5.9%), HPV35 (4.7%), HPV40 (4.7%), HPV45 (4.3%), HPV58 (4.0%), and HPV18 (3.6%) (Awua et al., 2020). The consistency between studies on the prevalence of identified genotypes strengthens the results and conclusions of this research. However, the dominance of non-vaccine HPV genotypes in this study and in other studies across SSA supports Dziva's claim that additional hr-HPV strains other than HPV 16 and 18 may have a larger influence on the development of CC in SSA (Dziva Chikwari, 2021).

According to the Ghana HPV and Related Disease Report, HPV59 (24.4%) is the third most common genotype, trailing only HPV18 (35.1%) and HPV 45 (25%) among WLHIV with invasive CC (Bruni et al., 2019; L. Bruni et al., 2019). Again, HPV-35 was the most prevalent genotype found and was substantially linked with HSIL in a study done in Ghana among WLHIV and HIV-negative women (Obiri-Yeboah. et al., 2017). Considering the data obtained from this study in comparison with others enumerated, hr-HPV59 and HPV35 pose a risk to WLHIV. Nevertheless, HPV59 and 35 are not encompassed in any of the current HPV vaccines, but make up a combined prevalence of 76.6% in this study (Table 5). This suggests that existing vaccines might not work perfectly against WLHIV harboring these genotypes.

The recent advent of a nano-valent vaccine may result in a change in vaccine preference among countries, particularly those that are yet to implement widespread or routine vaccination programs such as Ghana. HPV vaccines provide specific genotype protection (Lowy, 2016), hence, knowing the genotype circulation in a population has consequences for vaccine

selection and projected impact. In West Africa, data on prevalence of HPV on large population are scarce, and the use of different HPV genotyping methods hinder direct comparison (Bruni et al., 2018). In a review by Clifford et al., HPV16,18 and 45 were the most prevalent types among WLHIV diagnosed with invasive CC in Africa (Clifford et al., 2017), which agrees with the systematic review by Okoye et al., who reported HPV genotypes 16, 18 and 45 as the most prevalent among HIV seropositive and HIV seronegative women in the sub-region (Okoye et al., 2021). The prevalence ofHPV-18 was higher than HPV 16 in this study. This contrast the 3.3% prevalence of HPV 16 and HPV 18 that was found among women with healthy cervixes (Awua et al., 2020; Brandful et al., 2014)

Even though the prevalence of individual genotypes vary, previous data show that the most frequent genotypes discovered in our research are also prevalent in women with healthy cytology, or worse in other African nations (Ardhaoui et al., 2016). To better comprehend the major variables that contribute to HPV distributions globally, local variances in HPV patterns must be continually researched. However, it is possible that the kind of testing method employed impact the prevalence of specific HPV genotype. In this study, it was found that duration of ART and viral load (p=0.001) were strongly associated with HIV/HPV co-infection. This implied that the odds of WLHIV whose viral loads were above 1000 copies/ml were at higher risk of HPV infection as compared to women whose viral loads were less than 1000 copies/ml.

Hr-HPV 16/18 infection among study participants

The detection of HPV-16 and HPV-18, the two most prevalent high-risk genotypes included in current vaccine coverage, is an essential topic that many HPV researchers strive to answer. The findings of this study recorded 37.6% prevalence for HPV 16/18 which is by far above what has been recorded from a study in Kumasi (6.2%) (Donkoh, 2015) and Accra (6.6%-8.2%) (Brandful et al., 2014). Multivariate logistic regression analysis showed an association between the number of pregnancies and HPV 16/18 infections (p=0.049). Thus, the number of pregnancies was found to influence HPV 16/18 transmission among WLHIV. However, the odds of women who had one to three pregnancies were 91% less likely to have HPV 16/18 infections (AOR=0.09, 95% CI: 0.01-0.92, p=0.043) as compared to those who had seven or more pregnancies (AOR=0.05(0.00-0.65, p=0.022). More than 50%, 70% and 81.5% of HSIL, invasive CC and adenocarcinomas respectively are caused by HPV-16/18 (Donkoh; et al., 2022) hence, there is a great call for informed vaccine choices that target HPV 16/18 as a primary intervention in CC development among WLHIV.

Multiple hr-HPV co-infection among study participants

Many molecular epidemiology investigations (Carrillo-García et al., 2014; Covert et al., 2019) have shown that of multiple HPV genotypes increases the frequency of high-grade lesions and invasive CC (Bobadilla et al., 2019). This was subsequently verified in a Costa Rican study of 5,871 sexually active females between the ages of 18 and 25 years (Chaturvedi et al., 2011). Chaturvedi et al., found that women with multiple hr-HPV infections had a considerably higher incidence of CIN2+ and HGSIL+ than women with

single infections (Chaturvedi et al., 2011). Among HIV seropositive women, multiple hr-HPV infections are mostly reported (Looker et al., 2018). In this study, 60.3% of the women infected with hr-HPV had multiple hr-HPV infections. This was less compared with 75.7% obtained in North Africa among HIV seropositive populace but higher than 57.1% obtained among HIV seronegative women (Belglaiaa et al., 2015). Similarly, a 65.4% prevalence of multiple hr-HPV infections was recorded among Moroccan women diagnosed with HPV infection (Belglaiaa et al., 2015). Nevertheless, the prevalence of multiple hr-HPV obtained in this study may not completely reflect the population recruited for this study. Multiple hr-HPV infection elevates the risk of being infected with additional types of HPV (Goodman et al., 2008) and thus reduces the survival rate of CC patients but increases tumor recurrence (Kaliff et al., 2018). Similarly, nano-valent vaccine types HPV 16, HPV 18, HPV 31, HPV 33, HPV 45, HPV52 and HPV58 constituted a prevalence of 66% among women with multiple hr-HPV infection in this study. The current findings project that WLHIV with multiple hr-HPV infections should be continuously monitored and primary prevention of HPV among WLHIV could be achieved through the integration of nano-valent HPV vaccine program with HIV programs for WLHIV.

Chapter summary

This chapter presented and discussed results obtained by comparing and contrasting findings with previous research studies within the sub-region and beyond. Study respondents' general knowledge of CC was low and the prevalence of hr-HPV among WLHIV was 42.7% (95% CI: 37.4-48.1). The number of pregnancies and viral load were associated with HPV 16 and/or18

infection. Also, the level of education was found to be a key contributor to cervical cancer knowledge among the study participants. The total prevalence of hr-HPV was found to be 42.7%. hr-HPV 59 and HPV35 genotypes were found to be part of the top 5 prevalent HPV.About60.3% of women with hr-HPV had multiple hr-HPV with 44% of women having 2 to5 different genotypes of hr-HPV infections.

CHAPTER FIVE

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

Introduction

This chapter presents the summary and conclusions for the study as well as suggested recommendations that will help improve public health intervention in the timely prevention of hr-HPV in vulnerable groups such as WLHIV through the 90-70-90 strategies.

Summary

A total of 330 WLHIV were recruited for the study. Well-structured questionnaires were used in gathering the socio-demographic and behavioral diagnosis, prevention/treatment, reproductive health and other characteristics of the study populace. Also, the Atilla Biosystems Ampfire systems was used in screening the study populace for hr-HPV, multiple hr-HPV and HPV 16 and/or 18. All data were analyzed using Stata v.16 and the results were displayed in tables and diagrams. The categorical sociodemographic factors of research participants were described using frequencies and percentages. The means and standard deviations of continuous and normally distributed sociodemographic variables were utilized to characterize them. Frequencies, percentages, and charts were used to examine high-risk HPV prevalence and genotype types among HIV/HPV co-infected women. The association between cervical cancer knowledge and women's sociodemographic and behavioral characteristics, the association between study participants' HPV 16 and/or 18 genotype status and sociodemographic, knowledge, and behavioral variables, and the association between HIV/HPV co-infection and study participants' sociodemographic and behavioral characteristics were all investigated using

Chi-square tests. Every statistical test was two-sided, and a p-value of 0.05 or less was considered statistically significant. Age and viral load were considered a priori characteristics. As a result, age and viral load p-values were incorporated in a logistic regression analysis regardless of whether they were less than 0.1.

The mean age of the study participants was 47 (SD ±10.7) with the majority (32.4%) between the age of 45 to54. Most of the women could read as 39.4% had secondary education. There was a significant association between educational level (<0.001), the number of pregnancies (p=0.038) and awareness of cervical cancer screening (<0.001) of the study populace with their cervical cancer knowledge. Women with tertiary education were seven times more likely of having sufficient knowledge of cervical cancer as compared to those without formal/primary education (AOR=7.55, 95% CI: 1.34-42.43, p=0.022).

A total of 141 of the women were co-infected with HPV constituting a prevalence of 42.7%. HPV59 (50.4%), HPV18(30.5%), HPV35 (26.2%), HPV58 (17%) and HPV45 (14.9%) were the top 5 most prevalent genotypes. Multiple hr-HPV infections constituted 60.3%. 44% of women had 2 to5 multiple hr-HPV infections and 37.6% having HPV 16 and/or 18 infections. Multiple hr-HPV infections did not significantly correlate with the sociodemographic or behavioral attributes of the research population. . However, an association was established between HPV 16 and/or 18 infection and women's knowledge of cervical cancer screening accessibility (p=0.009). Also, the odds of having 1 to3 (AOR=0.09, 95% CI: 0.01-0.92, p=0.043), 4 to6 (AOR=0.07, 95% CI: 0.01-0.73, p=0.026) and seven or more pregnancies

(AOR=0.05, 95% CI: 0.00-0.65, p=0.022) were respectively 91%, 93% and 95% less likely to have HV 16/18 genotype as compared to those who had no pregnancy. Women with HIV viral loads above 1000copies/ml were more likely of having HIV/HPV co-infection compared with those with viral loads less than 1000copies/ml.

Conclusion

The t general knowledge of study participants' of HPV and CC was low. The overall prevalence of hr-HPV in the study populace was 42.7% (95% CI: 37.48.1). The common hr-HPV genotypes found were HPV 59, 35 and 45. The prevalence of non-vaccine types such as HPV 59 and 35 hr-HPV is an indication of a change in epidemiology in terms of hr-HPV genotype distribution among WLHIV and would inform policy decision making in vaccine choices for WLHIV in CCTH. Multiple genotype infection rate is high among these Ghanaian WLHIV, suggesting that viral suppression through effective ART may reduce the risk of being co-infected with HPV and HIV. Viral load of WLHIV < 1000 copies/ml and number of pregnancies were associated with HIV/HPV coinfection and HPV 16/18 infection respectively.

Recommendation

1. Effective HIV care at the clinics to ensure HIV viral suppressions should continue for WLHIV
2. To raise awareness of cervical cancer, educational materials on the prevalent hr-HPV genotypes should be made available in appropriate languages at the ART clinic.
3. Cervical cancer screening related counselling should be integrated into reproductive health education.

4. There should be efforts at the facility level to ensure routine offer of cervical cancer screening to the women during their ART clinic visits.
5. At the regional level, awareness creation efforts should be scaled up to all ART clinics through collaborate on with the regional health directorate and regional HIV coordinator.
6. There is need for more epidemiological and interventional to explore the barriers to screening among these WLHIV to inform policy directions in Ghana
7. The National/AIDS control programme should have the evidence from local studies collated to ensure they can be guided by data to make a case for financial support for CC prevention for WLHIV.
8. The government policies should prioritize educational programs on HPV and cervical cancer risk factors via media channels such as television and radio in various local languages to increase awareness in the general populace.
9. There is need for the national cervical cancer prevention policy for Ghana to include considerations for WLHIV.
10. The potential role of HPV vaccination for these women needs to be explored further.

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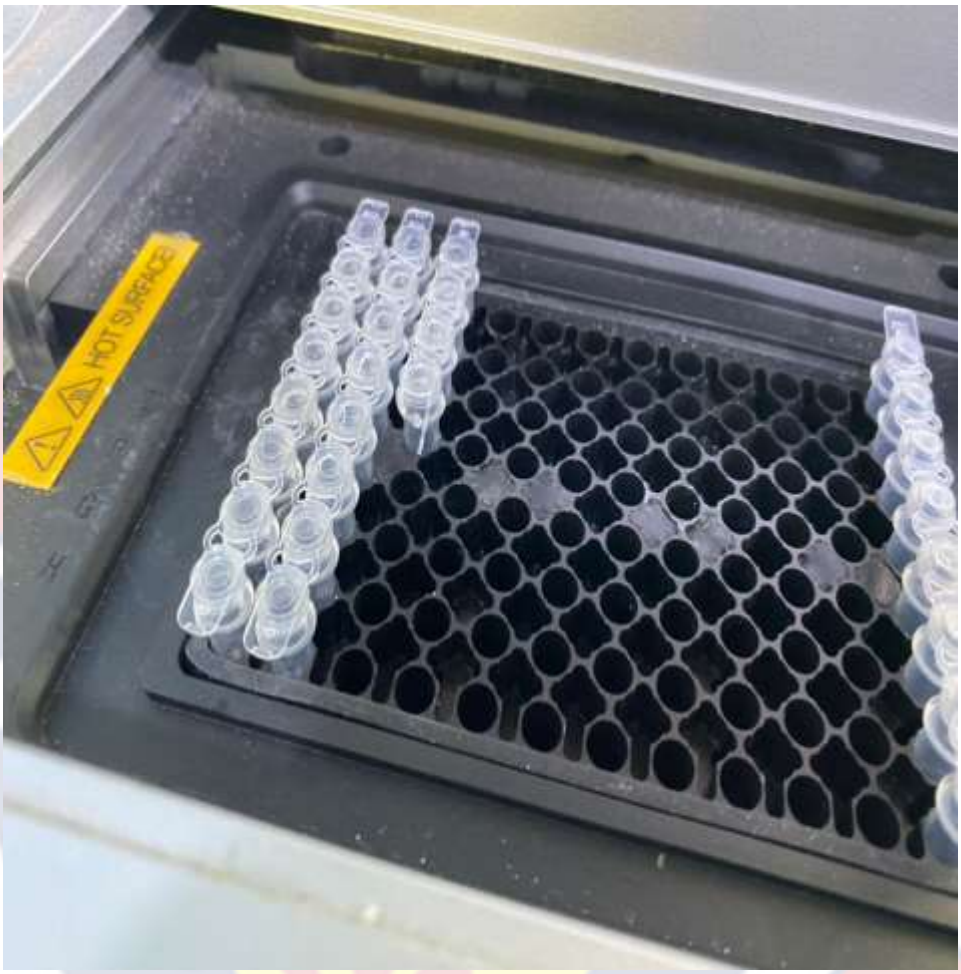
APPENDICES

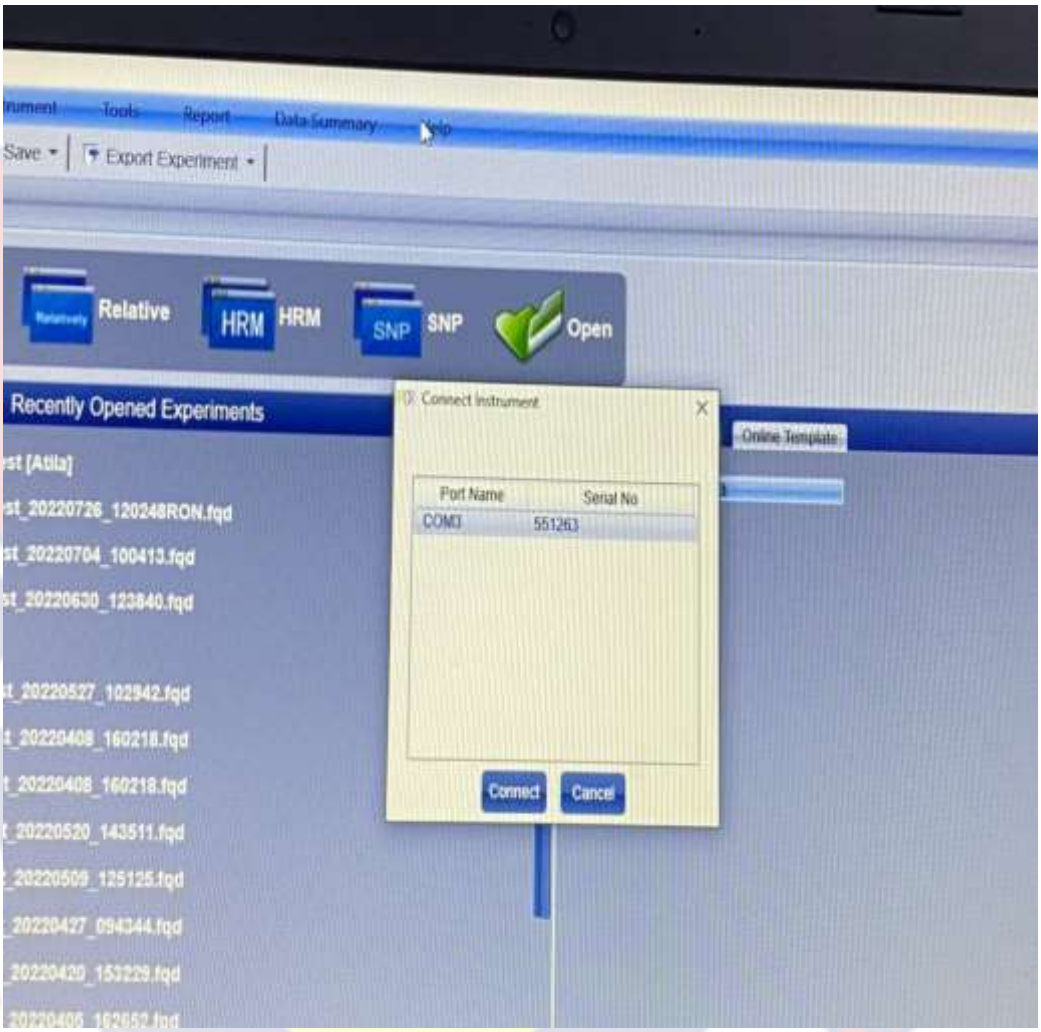
Appendix I: The Atilla Biosystems AmpFire System device

Appendix II: Primers PM-1, PM-2, PM-3 and PM-4 together with PC and NC on sample racks

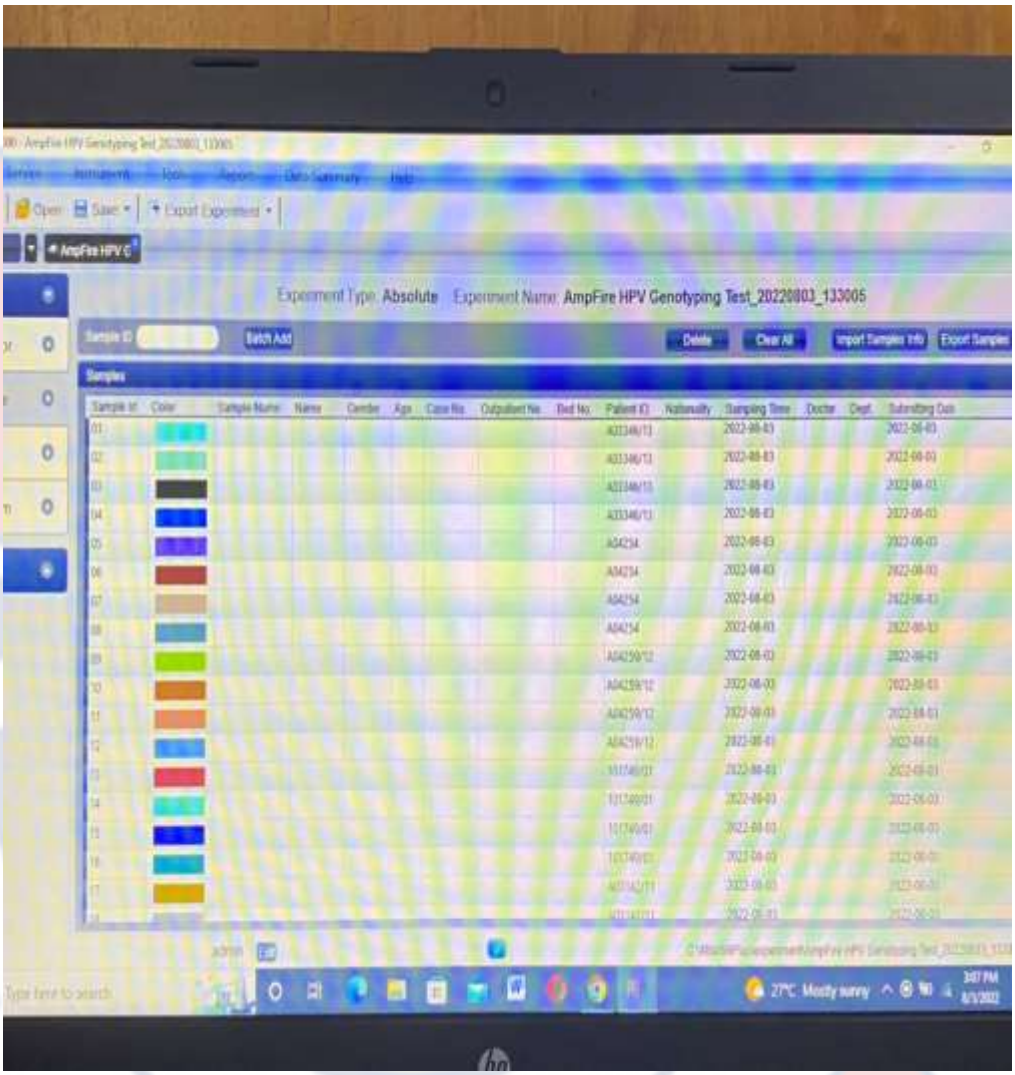
Appendix III: HPV samples, PC and NC loaded unto wells of the Atila Biosytems' thermal cycler



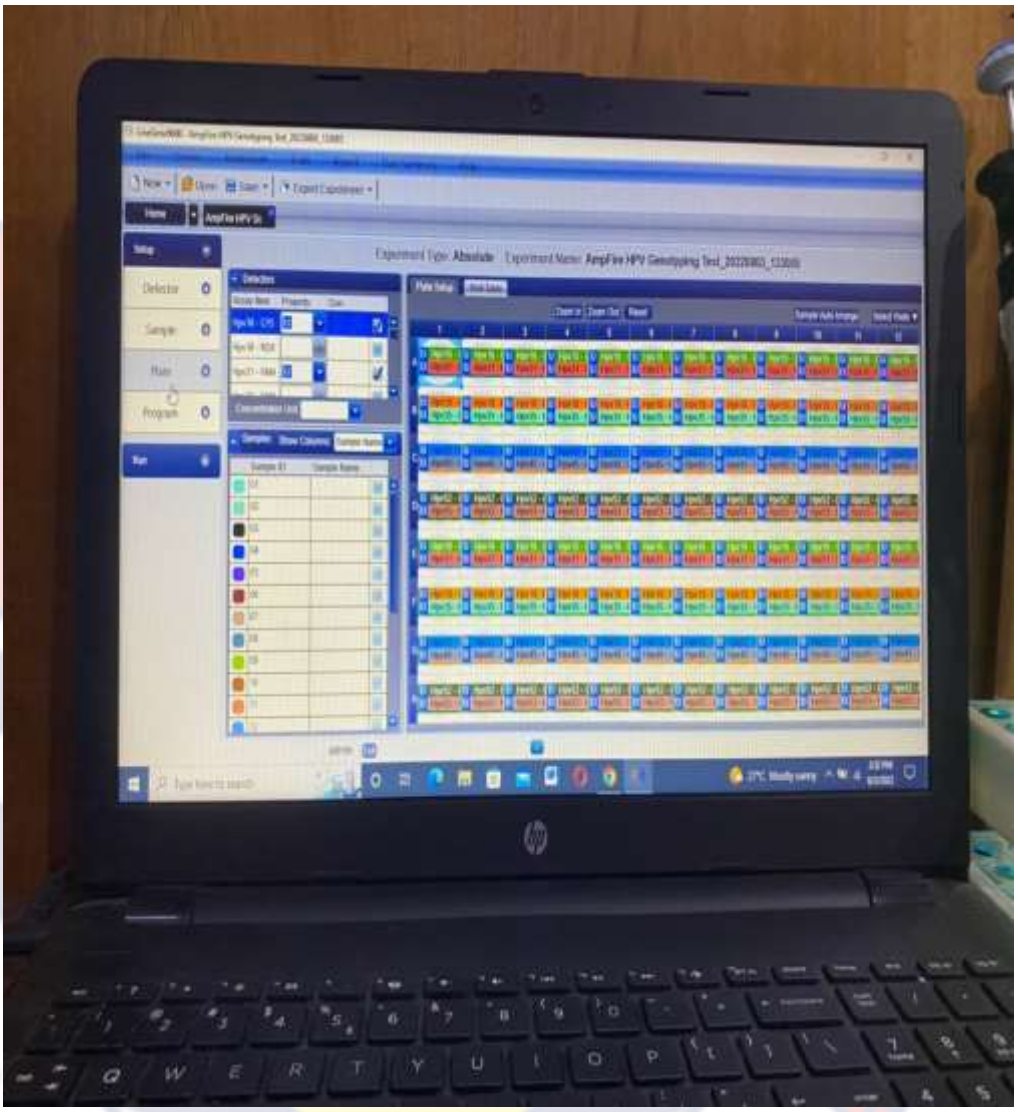
Appendix IV: HPV sample details inputed into the Atila Biosystems' software



Appendix V: An interface of HPV test run and the duration each test takes to be completed



Appendix VI: Interface of a complete test run



Appendix VII: Preparation of Lysis Buffer and Master Mix

Preparation of Lysis Buffer.

4mls of the Dry Swab Sample Buffer or 1X Lysis buffer (LB) was prepared from the 20X stock lysis buffer as follows: 200µl of the 20X LB was pipetted using a 1000µl micropipette into a 5ml Eppendorf tube. 3.8ml or 3800µl of distilled water was pipetted into the mixture in the Eppendorf tube. The mixture was gently vortexed and stored at room temperature.

Preparation of Master Mix

Four different master mix for four different primers were prepared for ninety-six samples two of which were positive control (PC) and negative control (NC) respectively. The formula (N+1) ×12=--------ul was used in measuring the reaction mixture and (N+1) ×11------ul for the primer mixture. For primer one master mix (PM-1 master mix) for 88 samples and eight controls, (96+1) ×12=1164ul of the reaction mix was measured into a 5ml Eppendorf tube. (96+1) ×11=1067ul of the primer mix was pipetted into the reaction mix in the Eppendorf tube. The mixture was gently vortexed. The same procedure was repeated for master mix for primer-2 (PM-2), primer 3 (PM-3) and primer 4 (PM-4). Each master mix for the respective primers were vortexed gently.

Appendix VIII: Questionnaire

Comprehensive and Sustainable Cervical Cancer Prevention Programme; a Pilot at Cape Coast Teaching Hospital		
No.	**Name of interviewer:** **Date:**	**Participant Code:** **Telephone number:**
	Question	**Participants Response**
SECTION A: Socio-Demographic		
A1	Age: (write the actual number in years)	
A2	Occupation	1. Unemployed 2. Trader/ Unskilled work 3. Civil servant 4. Health personnel 5. Other (specify)……
A3	Religion	1. Christianity 2. Islam 3. Traditional 4. Other (specify)……
A4	Marital status	1. Single 2. Married 3. Cohabiting 4. Divorced 5. Widow
A5	Level of education	1. No formal education 2. Primary 3. J.S.S/Middle school form 4 4. Secondary 5. Tertiary 6. Other (specify)…….
SECTION B: Reproductive health and other characteristics		
B1.	How many pregnancies have you had in the past? If the answer is 0 then skip **B2** *(Write the actual number)*	
B2.	How many children do you have? *(write the actual number down)*	
B3.	What is your HIV status *(if negative or don't know, skip question **B4 and Section E**)*	1. Positive 2. Negative 3. Don't Know
B4.	How long has it been since you were diagnosed? *(write the actual number down in months)*	
B5.	How many sexual partners have you had in your whole life? If 0 skip B6-B8*(Write the actual number)*	
B6.	How old were you when you had your first sexual intercourse? *(Write the actual number)*	
B7.	Are you currently sexually active? (if no skip **B8**)	1.Yes 2. No
B8.	Do you use condoms regularly when having sexual intercourse with your partner?	1.Yes 2. No

B09.	Have you used any of the following hormonal contraceptive before? *Tick all that apply and If non skip B10*	1. Oral 2. Injectable (monthly) 3. Injectable (3 monthly) 4. Implant 5. None
B10.	Are you currently on the hormonal contraceptive**?**	1. Yes 2. No
B11.	How old were you when you started menstruating? *(Write the actual number in years)*	
B12.	Are you still menstruating?	1. Yes 2. No
B13.	Do you currently smoke?	1. Yes 2. No
SECTION C: Knowledge about HPV		
C1	Have you ever heard about Human Papilloma Virus (HPV)? If no skip C2-C6	1. Yes 2. No
C2	Can men be infected with HPV?	1. yes 2. no 3. Unsure
C3	How is HPV transmitted? (Tick all that apply)	1. Oro-faecal 2. Respiratory droplets 3. Sexual
C4	HPV causes cervical cancer	1. Yes 2. No 3. Unsure
C5	Did you know about HPV vaccination before today? If no skip C6	1. Yes 2. No
C6	Can a person get HPV vaccine in Ghana?	1. Yes 2. No 3. Don't know
Section D: Knowledge about cervical cancer		
D1	Cervical cancer (cancer of the neck of the womb) is rare in Ghana	1. Yes 2. No 3. Unsure
D2	If there are women (blood relatives) in your family, who have had cervical cancer, it is more likely that you would also get it.	1. Yes 2. No 3. Unsure
D3	Using herbs in the vagina makes you more likely to get cervical cancer	1. Yes 2. No 3. Unsure
D4	Having an abortion or miscarriage makes you more likely to get cervical cancer	1. Yes 2. No 3. Unsure
D5	Which of these do you think can be signs of cervical cancer? (Tick all that apply)	1= Yes, 2= No, 3=Don't know
		Bleeding after sex
		Smelly discharge from the vagina
		Bleeding in-between menstrual periods
		Itching of the vagina
		No symptoms

D6	Cervical cancer is always fatal, even if caught at the early stages	1. Yes 2. No 3. Unsure
D7	Cervical cancer can be prevented	1. Yes 2. No 3. Unsure
D8	Have you ever heard of cervical screening? If no skip D9	1. Yes 2. No 3. Unsure
D9	What types of cervical screening do you know *(tick all that apply)?*	1. PAP smear 2. Visual Inspection with acetic acid 3. HPV test 4. Other (specify)… ……..… 5. Don't know
D10	Is it easy to get cervical cancer screening in Ghana?	1. Yes 2. No 3. Unsure
D11	Only women who have vaginal complaints should have cervical screening	1. Yes 2. No 3. Unsure
D12	Have you ever had cervical screening? If no skip D13	1. Yes 2. No
D13	If yes, what made you screen? *Please write the reason*	
Section E: HIV positive client's further details (obtained from the clinic booklet)		
E1	When was ART started *(state in months)*	
E2	Current ART regimen	
E3	Last (in the last 12 months) viral load (copies/ml)	
Section F: laboratory results		
F1	HR-HPV results *(tick all that were positive)*	Negative 16 18 31 33 35 39 45 51 52 53 56 58 59 66 68