Acceptability of Human Papillomavirus Self-Sampling among Women Living With Human Immunodeficiency Syndrome in Africa: A Systematic Review

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Certification

This is to certify that Olunike R. Abodunrin with Matriculation Number LCU/PG/001372 carried out this research work titled ''Acceptability of HPV Self-Sampling among Women Living with HIV in Africa: A Systematic Review'' in the Department of Public Health, Faculty of Basic Medical and Health Sciences, Lead City University, Ibadan, Oyo State, for the award of Master Degree (MPH) in Public Health and that this work has not been previously submitted.

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Dedication

This research is dedicated to GOD for the privilege and provision throughout the study and to all the women living with HIV/AIDS.

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Abstract

Human Papillomavirus self-sampling is a process in which a woman who wants to know if she has an HPV infection collects a cervicovaginal sample herself with a kit and sends it to a laboratory for analysis. Self-sampling has the potential to increase the uptake of cervical cancer screening among women living with HIV in Africa. Immunosuppression and low CD4 counts caused by HIV infection predispose women living with HIV infection to an increased risk for cervical cancer and the development of intraepithelial lesions. Although the majority of HPV infections are asymptomatic and cure on their own, chronic HPV infection can lead to illness. In women, persistent infection with specific HPV types (most often HPV-16 and HPV-18) can cause precancerous lesions that can proceed to cervical cancer if left untreated. The causal relation between HPV and cervical cancer has enabled self-sampling to be envisaged as a possible screening method in low-resource settings. Also, in Africa, research conducted on the acceptability of the self-sampling of HPV among HIV patients is few. The purpose of this study was to evaluate the acceptability of HPV self-testing among women living with HIV, the uptake of cervical cancer screening services, the frequency of cervical cancer screening, the clinical treatment provided for cervical lesions/HPV positive and the social harm/adverse effects of self-sampling. PubMed, Cochrane Central Register of Controlled Trials and Google Scholar were used to search for articles on HPV self-sampling among women living with HIV in Africa published as of 1 September 2020. The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2020 guidelines were followed to design and report the results. A total of 1074 records were identified through electronic searches. After applying the screening criteria, 7 studies were eligible for inclusion in the review and were analysed. Five articles reported the acceptability of self-sampled tests, five studies stated the participants that tested positive, only two reported follow-up, two studies reported social harm/adverse effects of self-clinician sampled test and no study reported the frequency of cervical cancer screening. HPV self-sampling is an effective and achievable substitute for clinician sampling in Africa. It could improve the uptake of cervical cancer screening and reduce the mortality rate of cervical cancer in Africa.

Keywords: Human papillomavirus, Self-sampling, women living with HIV/AIDS, Africa

Word counts: 367

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List of Acronyms

Abbreviations	Meaning
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
CC	Cervical Cancer
CD4	Cell Differentiating 4
CIN	Cervical Intraepithelial Neoplasia
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Syndrome
HPV	Human Papillomavirus
Hr HPV	High Risk Human Papillomavirus
WLHIV	Women Living with HIV
WHO	World Health Organization

Chapter One

Introduction

1.1 Background to the Study

HPV self-sampling is a process in which a woman who wants to know if she has an HPV infection collects a cervicovaginal sample herself with a kit and sends it to a laboratory for

analysis. HPV screening through patient self-collection has been shown to have a high sensitivity and specificity for the detection of high-risk HPV types which can lead to cervical cancer[1].

Clinician-sample collection is the process in which a clinician collects a cervicovaginal sample from a woman and sends it to the laboratory for analysis. While HPV self-sampling cannot provide a diagnosis of cervical precancer, it identifies those women at higher risk. The privacy afforded by self-sampling may encourage more people to get tested compared with Pap smears that, especially in LMICs, still have low coverage due to limited population awareness and lack of availability[1].

High levels of satisfaction result from women's acceptance of self-sampling. Universally, women would be willing to take their sampling themselves[2]. Concerns about screening and their acceptance of the self-sampling test include embarrassment at being examined by a male doctor, mistrust of the healthcare system, and various forms of misinformation about screening. The high acceptability of a self-sampled HPV test suggests that the approach can be effective at removing obstacles to conventional cervical cancer screening, regardless of the education levels of women or widely-held preconceptions[3].

The human immunodeficiency virus, also known as HIV, is an infection that destroys the immune system of the body, more specifically the CD4 cells of the white blood cells. HIV is responsible for the destruction of these CD4 cells, which in turn lowers a person's immunity against opportunistic diseases such as tuberculosis and fungal infections, as well as serious bacterial infections and some malignancies. According to UNAIDS, globally the prevalence of HIV is between 33.9 million–43.8 million[4]. Furthermore, Sub-Saharan Africa is the most severely impacted region in the world when it comes to HIV/AIDS, which continues to be a major worry for the health of people all over the world. There are approximately 25.6 million people living with HIV in Sub-Saharan Africa, which accounts for more than 70 percent of all

fatalities caused by AIDS and two-thirds of the recent total number of HIV infections across the entire world. It is quite unfortunate that more than half of the people who are infected with HIV in sub-Saharan Africa are children and women[5].

HPV infection is one of the most common sexually transmitted infections worldwide[1], with an estimated prevalence of approximately 12%, in a population of over one million asymptomatic women from 194 studies[2]. Around 90% of infected individuals are asymptomatic and clear the infection within two years[3]. Nevertheless, a small proportion develops a persistent infection that can lead to a wide range of diseases, from benign lesions to cancers in the anogenital area as well as some benign and cancerous oropharyngeal diseases[4].

More than 100 HPV genotypes with different tropism and pathogenesis have been identified to date. Mucosal HPV types can be classified into high- and low-risk types according to their capacity to induce cancer[5,6]. The low-risk types, HPV 6 and HPV 11 cause 90% of anogenital warts and benign/low-grade abnormalities in the genital areas[7] and are also responsible for causing recurrent respiratory papillomatosis, a proliferative disease of the upper aero-digestive track[8,9].

Cervical cancer remains the fourth most common female cancer globally, with an estimated 570,000 cases and 311,000 deaths yearly[10]; Carcinogenic types of HPV are responsible for up to 4.5% (630,000 cases) of all new cases (8.6% in females; 0.9% in males) and cause 29.5% of all HPV-related cancers[11, 12]. In particular, HPV 16 and 18 cause 70% of the cervical cancers, and a relevant proportion of vaginal (78%) and anal (88%), as well as some vulvar (25%) and penile (50%) cancers and, together with HPV types 31/33/45/52/58, are responsible for about 90% of HPV-related cancers worldwide[13].

In 2018, Africa contributed to far more than a quarter of all cervical cancer deaths, making cervical cancer the continent's biggest cause of death in women.[131, 132] The prevalence rate of cervical cancer is highest in Africa [33].

There is evidence that the protection elicited by HPV vaccines to prevent HPV persistence and HPV-associated diseases in women and men is robust and long-lasting and widespread immunization campaigns could lead to substantial health economic benefits[14]. Since 2006, HPV vaccination has been introduced globally into national immunization programs for girls in 71 countries, and boys in 11 countries[15].

Many countries with national immunization programs experienced difficulties in reaching HPV vaccination coverage goals due to several HPV vaccination uptake barriers, such as lack of knowledge about HPV infection and related diseases in vaccine targets, parents of pre-adolescents and multidisciplinary providers, vaccination safety concerns, criticisms in the accessibility to HPV vaccine due to the high cost, limited healthcare services, organizational aspects of HPV vaccine campaigns and difficulties in vaccine schedule completion for patients and providers[16,17]. These barriers are of particular concern in low- and middle-income countries, which bear the greatest global burden of HPV-related cancers, particularly cervical cancer[18].

In Nigeria, 23.7% of women in the general population are estimated to harbour HPV infection at any given time, and 90% of invasive cervical cancers are attributed to HPV 16 and 18[19]. Cervical cancer is preventable by early detection and treatment of the preinvasive stage and by the use of the HPV vaccine. Cervical cancer affects poor women in the least-developed countries more often and more aggressively due to a lack of available routine screening services and a high prevalence of other serious health conditions such as human immunodeficiency virus (HIV)[20].

With the widespread use of highly active antiretroviral therapy (HAART), the incidence of HIV-defining cancers such as Kaposi sarcoma and non-Hodgkin lymphoma has declined dramatically,

but cervical cancer rates have remained high among women living with HIV (WLHIV)[21]. Cohort studies in Canada and the United States have consistently shown that the risk of invasive cervical cancer is higher among WLHIV than in HIV-negative women[22],[23]. Other studies have confirmed that the prevalence of high-risk human papillomavirus (HR-HPV) infection is also higher and more persistent in WLHIV. There is general agreement that a long history of HIV infection and prolonged immunosuppression is associated with persistent HPV infection and invasive cervical cancer.

Studies have identified myriad barriers that deter WLHIV from accessing health care, including structural racism, HIV-related stigma, discrimination within and outside of the health care system[25], and criminalization of HIV non-disclosure[24]. Other studies show that the utilization of health services and the uptake of cancer screening among marginalized groups are associated with their health literacy[26]. These findings suggest that socially inclusive, innovative, and relevant strategies are needed to promote HPV and cervical cancer screening among WLHIV. Insights from studies on HIV self-testing suggest that HPV self-sampling is a potential strategy to effectively engage marginalized WLHIV[26]. Low individual uptake of cervical cancer screening is a major obstacle to reducing the morbidity and mortality of cervical cancer in Cameroon; data indicates only 19.7% of all women over the age of 18 have ever been screened for cervical cancer[27]. Many patient barriers may hinder compliance with screening guidelines, including but not limited to fear of positive results after screening, anxiety, discomfort surrounding the screening procedure, and cost of the test and/or transportation to the clinical setting [27]. As a move to address barriers, the option to self-collect vaginal or cervical samples is being promoted to increase participation in cervical cancer screening in South Africa.

Given the relevance of HPV infection and the burden of related diseases, the complexity of factors influencing the compliance to the HPV vaccine, the knowledge, attitudes, and practice of

cervical cytology are essential for the success of the campaign for the prevention and early detection of cervical cancer, especially among women living with HIV. The purpose of this study, therefore, is to describe the knowledge, attitudes, and practice of cervical cancer among women living with HIV in Nigeria, as well as to determine the acceptability of self-sampling among the same set of people.

Systematic reviews are a type of review that gathers secondary data and analyzes it using repeatable analytical techniques. Research questions can be broad or specific, and systematic reviews are one sort of evidence synthesis that identifies and synthesizes data that directly relates to the systematic review topic. A comprehensive overview of the most recent literature pertinent to a research question can be provided via a systematic review. A systematic review employs a strict and open method of research synthesis with the objective of evaluating and, where practical, reducing bias in the results. There are qualitative reviews and other types of mixed-methods reviews that follow guidelines for obtaining, assessing, and reporting evidence, even though many systematic reviews are founded on an explicit quantitative meta-analysis of the available data[6]. The results of appropriate investigations are occasionally combined using statistical techniques (meta-analysis) in systematic reviews of quantitative data or mixed-method reviews.

Africa is the second-largest continent in the globe in terms of both land and population. Only a minor land bridge in the northeast connects the African Mainland with Western Asia, making it a nearly totally isolated landmass. Around 30,244,000 km2 (11,700,000 mi2), or six percent of the world's total surface, is occupied by Africa. The continent, including the nearby islands, makes up around 20% of the planet's land area[7]. Algeria is the largest nation in Africa, followed by Sudan and the Democratic Republic of the Congo (Kinshasa). The second-largest continent is home to an estimated 1.37 billion people, or 14% of the world's population (in 2021). Nigeria, which has a population of more than 211 million, is by far the most populous nation in Africa[8].

1.2 Statement of the Problem

Human Papillomavirus is the most prevalent viral infection of the reproductive system, causing a variety of problems in both men and women, including precancerous lesions that can lead to cancer. Although the majority of HPV infections are asymptomatic and cure on their own, chronic HPV infection can lead to illness. In women, persistent infection with specific HPV types (most often HPV-16 and HPV-18) can cause precancerous lesions that can proceed to cervical cancer if left untreated [1]. In men and women, HPV infection is linked to oropharyngeal and anogenital cancers, as well as other disorders[29].

HIV infection causes immunosuppression and low CD4 levels, which puts HIV-positive women at a greater risk of cervical cancer. According to the Human Papillomavirus and Related Diseases Report 2019[28] . About 14,943 women are diagnosed with cervical cancer each year, with 10,403 dying from the disease28. Cervical cancer ranks as the 2nd most frequent cancer among women in Nigeria and the 2nd most frequent cancer among women between 15 and 44 years of age. Cervical HPV-16/18 infection is predicted to be present in 3.5 per cent of women in the general population at any given time, and HPVs 16 and 18 are responsible for 66.9% of invasive cervical cancers. Cervical cancer is best avoided by early detection and treatment of cancer and precancerous lesions. The incidence and mortality of cervical cancer have declined significantly in developed countries due to uptake of cervical cancer screening, but screening has not been as successful in low-middle-income countries. Self-sampling has the potential to increase the uptake of cervical cancer screening among women living with HIV in Africa. The awareness and knowledge of women living with HIV in Africa on self-sampling is poor compare to other developed countries with high uptake of cervical cancer screening through self-sampling, however, among those that are aware of self-sampling the acceptability is high[10].

1.3 Justification of the Study

Women with suppressed immune systems will benefit from the findings of the study if HPV self-sampling can be introduced to their routine care. The causal relation between HPV and cervical cancer has enabled self-sampling to be envisaged as a possible screening method in low-resource settings. Also, in Africa, research conducted on the acceptability of the self-sampling of HPV among HIV patients is few.

1.4 Aim and Objectives of the Study

Aim

In Africa, the importance of HPV testing in cervical cancer screening is crucial, as screening is the major method for reducing the burden of cervical cancer until the benefits of HPV vaccination become recognized[34]. This study aims to systematically assess the acceptability of HPV self-testing among women living with HIV in Africa.

1.4.1 Specific Objectives

1 Evaluate the uptake of cervical cancer screening services in Africa.

2 Assess the frequency of cervical cancer screening

3. The social harm/adverse effects using the kit

1.4.2 General Objectives

To assess the clinical assessment and treatment of the cervical lesion for HIV positive patients.

1.5 Research Question

1. Do women of reproductive age living with HIV in Africa accept HPV self-sampling?
2. Is there social harm/ adverse effects when women living with HIV/AID use self-sampling kit?

1.6 Significance of the Study

The study will provide important information on the acceptability of HPV self-testing for women living with HIV. Also, it will elaborate on the importance of self-sampling among women living with HIV in Africa and how it will reduce the prevalence of cervical cancer. Furthermore, it will emphasis on the integration of HPV self-sampling into routine HIV care

1.7 Scope of the Study

The research will focus on articles on HPV self-sample testing among women living with HIV. Women living with HIV were identified to be at high risk of developing pre-cancerous lesions in the cervix, which if left untreated, can develop into cervical cancer. The research will review their acceptability, compare HPV self-sampling, and uptake of cervical cancer screening among women living with HIV.

1.8 Limitation of the Study

Only few of the studies gave indices of their participants acceptability to either self-sampling or clinician sampling and there are no data published from Nigeria on acceptability of HPV self-sampling among women living with HIV.

1.9 Operational Definition of Terms

Women living with HIV: These are women whose HIV status are known to be positive

Self-Sampling Collection: Self-sampling is a process in which a woman who wants to know if she has an HPV infection collects a cervicovaginal sample herself with a kit and sends it to a laboratory for analysis.

Acceptability of HPV Self-sampling: This refers to satisfactoriness derived from collecting samples by oneself.

Endnotes

1. Yeh, Ping Teresa, Caitlin E. Kennedy, Hugo De Vuyst, and Manjulaa Narasimhan. 2019. "Self-Sampling for Human Papillomavirus (HPV) Testing: A Systematic Review and Meta-Analysis." *BMJ Global Health* 4, no. 3. https://doi.org/10.1136/bmjgh-2018-001351.

2. Lofters, Aisha, Kimberly Devotta, Vijayshree Prakash, and Mandana Vahabi. 2021. "Understanding the Acceptability and Uptake of Hpv Self-Sampling amongst Women under-or Never-Screened for Cervical Cancer in Toronto (Ontario, Canada): An Intervention Study Protocol." *International Journal of Environmental Research and Public Health* 18, no. 17: 1–11. https://doi.org/10.3390/ijerph18179114.

3. Rosenbaum, Alan J., Julia C. Gage, Karla M. Alfaro, Lauren R. Ditzian, Mauricio Maza, Isabel C. Scarinci, Juan C. Felix, et al. 2014. "Acceptability of Self-Collected versus Provider-Collected Sampling for HPV DNA Testing among Women in Rural El Salvador." *International Journal of Gynecology and Obstetrics* 126, no. 2: 156–60. https://doi.org/10.1016/j.ijgo.2014.02.026.

4. UNAIDS. 2021. "Global HIV Statistics." *Fact Sheet 2021*, no. June: 1–3.

5. Amuche, Nweze Justus, Eke Ifeanyichukwu Emmanuel, and Nweze Emeka Innocent. 2017. "HIV/AIDS in Sub-Saharan Africa: Current Status, Challenges and Prospects." *Asian Pacific Journal of Tropical Disease* 7, no. 4: 239–56. https://doi.org/10.12980/apjtd.7.2017D6-366.

6. Nunn, Jack, and Steven Chang. 2020. "What Are Systematic Reviews?" *WikiJournal of Medicine* 7, no. 1: 1–11. https://doi.org/10.15347/wjm/2020.005.

7. Nationsonline.org. 2021. "List of African Countries - Nations Online Project." Www.nationsonline.org.https://www.nationsonline.org/oneworld/africa.htm

8. Gottlieb, Sami L., and Christine Johnston. 2018. "Future Prospects for New Vaccines against Sexually Transmitted Infections." *Current Opinion in Infectious Diseases*, December (December), 1. https://doi.org/10.1097/qco.0000000000000343.

9. Adams, Abdul Rashid, Priscilla Awo Nortey, Benjamin Ansah Dortey, Richard Harry Asmah, and Edwin Kwame Wiredu. 2019. "Cervical Human Papillomavirus Prevalence, Genotypes, and Associated Risk Factors among Female Sex Workers in Greater Accra, Ghana." *Journal of Oncology* 2019, no. June (June): 1–7. https://doi.org/10.1155/2019/8062176.

10. El-Zein, Mariam, Agnihotram V. Ramanakumar, Paulo Naud, Cecilia M. Roteli-Martins, Newton S. de Carvalho, Paola Colares de Borba, Julio C. Teixeira. 2019. "Determinants of Acquisition and Clearance of Human Papillomavirus Infection in Previously Unexposed Young Women." *Sexually Transmitted Diseases* 46, no. 10 (October): 663–69. https://doi.org/10.1097/OLQ.0000000000001053.

11. Toh, Zheng Quan, Jennie Kosasih, Fiona M Russell, Suzanne M Garland, Edward K Mulholland, and Paul V Licciardi. 2019. "Recombinant Human Papillomavirus Nonavalent Vaccine in the Prevention of Cancers Caused by Human Papillomavirus." *Infection and Drug Resistance* Volume 12, no. July (July): 1951–67. https://doi.org/10.2147/idr.s178381

12. Mirabello, Lisa, Megan Clarke, Chase Nelson, Michael Dean, Nicolas Wentzensen, Meredith Yeager, Michael Cullen, Joseph Boland, Mark Schiffman & Robert Burk. 2018. "The Intersection of HPV Epidemiology, Genomics and Mechanistic Studies of HPV-Mediated Carcinogenesis." *Viruses* 10, no. 2 (February): 80. https://doi.org/10.3390/v10020080.

13. Pinheiro, Maisa, Ariana Harari, Mark Schiffman, Gary M. Clifford, Zigui Chen, Meredith Yeager, Michael Cullen, 2021. "Phylogenomic Analysis of Human Papillomavirus Type 31 and Cervical Carcinogenesis: A Study of 2093 Viral Genomes." https://doi.org/10.3390/v13101948.

14. Domenech-Viñolas, Marta, Leith León-Maldonado, Paula Ramírez-Palacios, Yvonne N. Flores, Víctor Granados-García, Brandon Brown, Edgar Corona 2018. "Incidence, Psychosocial Burden, and Economic Impact of Genital Warts in Mexico." *Salud Pública de México* 60, no. 6 (December): 624–32. https://doi.org/10.21149/10008.

15. "Recurrent Respiratory Papillomatosis: Background, Pathophysiology, Epidemiology." 2020. *EMedicine*, March (March). https://emedicine.medscape.com/article/302648-overview.

16. Fortes, Helena Ribeiro, Felipe Mussi von Ranke, Dante Luiz Escuissato, Cesar Augusto Araujo Neto, Gláucia Zanetti, Bruno Hochhegger, Carolina Althoff Souza, and Edson Marchiori, 2018. "Recurrent respiratory papillomatosis: a state-of-the-art review." Respiratory medicine 126 (2017): 116-121.

17. Bray, Freddie, Jacques Ferlay, Isabelle Soerjomataram, Rebecca L. Siegel, Lindsey A. Torre, and Ahmedin Jemal. "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries." CA: a cancer journal for clinicians 68, no. 6 (2018): 394-424.

18. Martel, Catherine de, Damien Georges, Freddie Bray, Jacques Ferlay, and Gary M Clifford. 2020. "Global Burden of Cancer Attributable to Infections in 2018: A Worldwide Incidence Analysis." *The Lancet Global Health* 8, no. 2 (February): e180–90. https://doi.org/10.1016/s2214-109x(19)30488-7.

19. Medeiros, Rita, Susan Vaz, Teresa Rebelo, & Margarida Figueiredo-Dias 2020. "Prevention of human papillomavirus infection. Beyond cervical cancer: A brief review." Acta medica portuguesa 33, no. 3 (2020): 198-201.

20. Liu, Fang, Li Chang, Ting Bai, Xiaojuan Liu, & Jinliang Hu. 2021. "Association of Human Papillomavirus Genotype Distribution and Cervical Cytology: A Cross-Sectional Study." *Epidemiology and Infection* 149. https://doi.org/10.1017/s0950268821000741.

21. Prue, Gilliam, Peter Baker, Donna Graham, Chris Nutting, Peter Greenhouse, and Mark Lawler 2018. "It is time for universal HPV vaccination." The Lancet 392, no. 10151 (2018): 913-914.

22. Mondiale de la Santé, Organisation, & World Health Organization 2017. "Human papillomavirus vaccines: WHO position paper, May 2017." Weekly Epidemiological Record= Relevé épidémiologique hebdomadaire 92, no. 19 (2017): 241-268.

23. Shinkafi-Bagudu, Zainab. 2020. "Global Partnerships for HPV Vaccine Must Look beyond National Income." *JCO Global Oncology*, no. 6 (November): 1746–48. https://doi.org/10.1200/go.20.00504.

24. Dorji, Thinley, Tanawin Nopsopon, Saran Tenzin Tamang, and Krit Pongpirul. 2021. "Human Papillomavirus Vaccination Uptake in Low-and Middle-Income Countries: A Meta-Analysis." *EClinicalMedicine* 34, no. April (April): 100836. https://doi.org/10.1016/j.eclinm.2021.100836.

25. Toh, Zheng Quan, Paul V. Licciardi, Fiona M. Russell, Suzanne M. Garland, Tsetsegsaikhan Batmunkh, & Edward K. Mulholland 2017. "Cervical cancer prevention through HPV vaccination in low-and middle-income countries in Asia." Asian Pacific journal of cancer prevention: APJCP 18, no. 9 (2017): 2339.

26. World Health Organization. 2022. "Cervical Cancer." Www.who.int. February 22, 2022. https://www.who.int/news-room/fact-sheets/detail/cervical-cancer.

27. World Health Organization. Consolidated guidelines on sexual and reproductive health and rights of women living with HIV. World Health Organization, 2017.

28. Ghebre, Rahel G., Surbhi Grover, Melody J. Xu, Linus T. Chuang, & Hannah Simonds, 2017. "Cervical cancer control in HIV-infected women: past, present and future." Gynecologic oncology reports 21 (2017): 101-108.

29. Stelzle, Dominik, Luana F. Tanaka, Kuan Ken Lee, Ahmadaye Ibrahim Khalil, Iacopo Baussano, Anoop S. V. Shah, David A. McAllister, 2020. "Estimates of the Global Burden of Cervical Cancer Associated with HIV." *The Lancet Global Health* 0, no. 0 (November). https://doi.org/10.1016/S2214-109X(20)30459-9.

30. Luo, Qianlai, Anna Satcher Johnson, H Irene Hall, Elizabeth K Cahoon, and Meredith Shiels. 2020. "Kaposi Sarcoma Rates among Persons Living with Human Immunodeficiency Virus in the United States: 2008—2016." *Clinical Infectious Diseases* 73, no. 7 (November): e2226–33. https://doi.org/10.1093/cid/ciaa999.

31. Kronfli, Nadine, Ashley Lacombe-Duncan, Ying Wang, Alexandra de Pokomandy, Angela Kaida, Carmen Logie, Tracey Conway 2017. "Access and engagement in HIV care among a national cohort of women living with HIV in Canada." Aids Care 29, no. 10 (2017): 1235-1242.

32. Logie, Carmen H., Nina Sokolovic, Mina Kazemi, Stephanie Smith, Shaz Islam, Melanie Lee, Rebecca Gormley, Angela Kaida, Alexandra Pokomandy, and Mona Loutfy. 2022. "Recent Sex Work and Associations with Psychosocial Outcomes among Women Living with HIV: Findings from a Longitudinal Canadian Cohort Study." *Journal of the International AIDS Society* 25, no. 3 (March). https://doi.org/10.1002/jia2.25874.

33. McGuire, Madison, Anna de Waal, Angela Karellis, Ricky Janssen, Nora Engel, Rangarajan Sampath, Sergio Carmona, Alice Anne Zwerling, Marta Fernandez Suarez, and Nitika Pant Pai. 2021. "HIV Self-Testing with Digital Supports as the New Paradigm: A Systematic Review of Global Evidence (2010–2021)." *EClinicalMedicine* 39, no. September (September). https://doi.org/10.1016/j.eclinm.2021.101059.

34. Ferlay, J., Colombet, M., Soerjomataram, I., Mathers, C., Parkin, D. M., Piñeros, M., ... & Bray, F. 2019. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. International journal of cancer, 144(8), 1941-1953.

35. Wentzensen, Nicolas, and Marc Arbyn. 2017. "HPV-Based Cervical Cancer Screening-Facts, Fiction, and Misperceptions." *Preventive Medicine* 98, no. May (May): 33–35. https://doi.org/10.1016/j.ypmed.2016.12.040.

Chapter Two

Literature Review

2.1 Human Papillomavirus Infection

The majority of the infections do not cause illness, persistent infection can result in disease. HPV infects nearly everyone at some point in their lives[34].

A illness known as human papillomavirus infection (HPV infection) is brought on by the Papillomaviridae family of DNA viruses, which includes the human papillomavirus (HPV).[31]

90% of HPV infections disappear on their own within two years and many of them have no symptoms at all[32]. Warts or precancerous lesions can develop when an HPV infection lasts for a prolonged period of time[35]. Depending on which site is affected, these lesions raise the risk of developing cancer of the cervix, vulva, vagina, penis, anus, mouth, tonsils, or throat[33, 34].

HPV can cause anogenital warts, recurrent respiratory papillomatosis, oropharyngeal cancer, and a variety of anogenital cancers in men and women (including penile, anal, vaginal, vulvar, and cervical cancers). Most sexually active persons will have detectable HPV at least once in their lifetime[40].

HPV is responsible for approximately all occurrences of cervical cancer; two strains, HPV16 and HPV18, constitute 70% of cases. However, almost 90% of HPV-positive oropharyngeal cancers are caused by HPV16[33]. HPV is related to between 60% and 90% of the various malignancies mentioned above[35]. HPV6 and HPV11 are the most common causes of genital warts and laryngeal papillomatosis[31].

There are about 170 different types of HPV[38]. Over forty different kinds can infect the anus and genitals through sexual contact.

2.1.1 Pathogenesis of HPV Infection and Cervical Cancer

The pathogenesis of HPV infection and Cervical Cancer occurs at the basal epithelium. Most infections, however, clear on their own after a year or two. Only a small percentage of infected people become infected for life; persistent infection is the most important risk factor for the development of cervical cancer.

Screening can detect squamous intraepithelial lesions (SIL) of the cervix in women. LSILs (low-grade squamous intraepithelial lesions) recur frequently. Cancer precursors are high-grade

squamous intraepithelial lesions (HSIL). Cervical intraepithelial neoplasia was the name given to these types of lesions before (CIN). Such cancer precursors can lead to cervical cancer years or decades later when they go undetected and untreated.

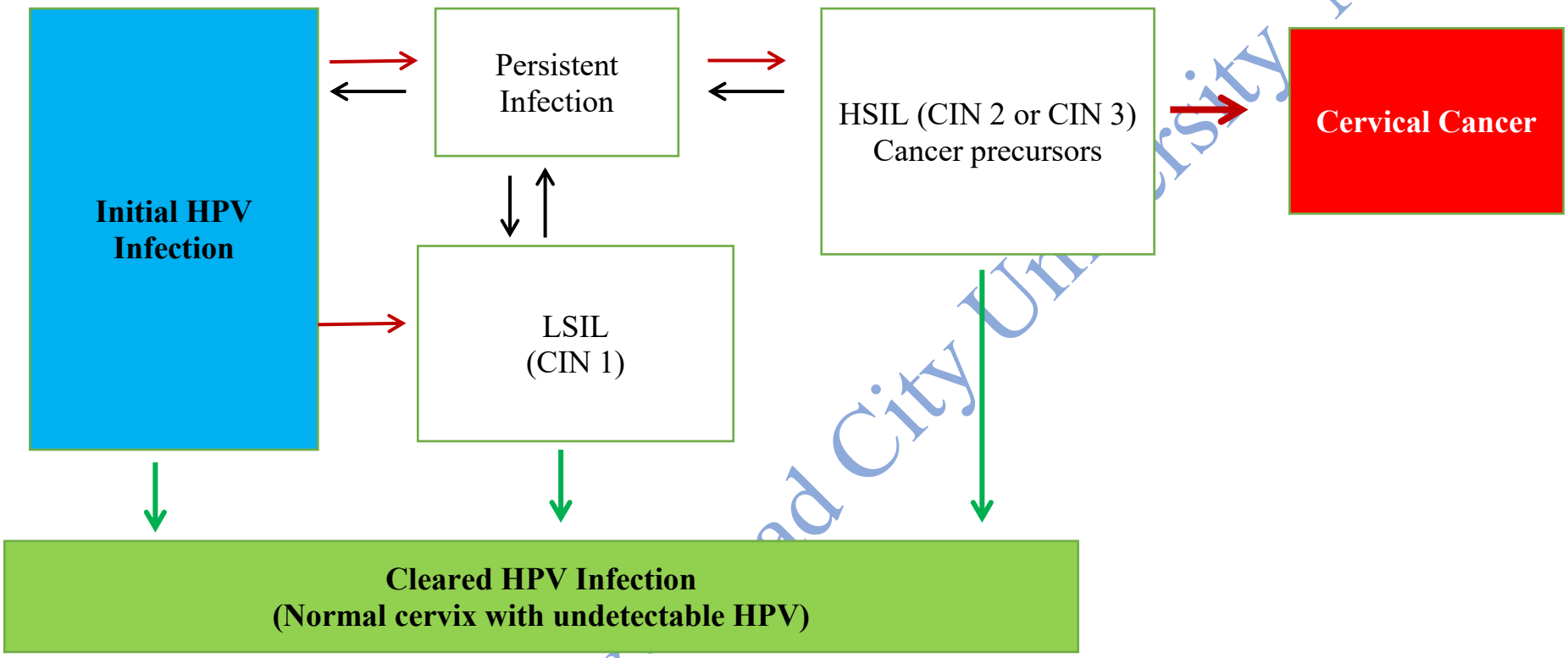


Figure 3.1: Pathogenesis of HPV Infection and Cervical Cancer

Source: (Song 2015)

2.2.1 Molecular Modalities of the HPV Infection Cycle

Numerous viral strains, including HPV 16, 18, and 31, were used in the majority of research characterizing the HPV infection cycle. The infection process, however, is still the same despite the genetic diversity and the related-diversified infection profile. Basal epithelial cells, which have a high mitotic potential and are undifferentiated deeper layer cells of the skin and/or mucous membranes, are the only cells that are infected by HPVs. Indeed, only through microlesions of these higher layer cells that develop during trauma may viruses that are present on the outer apical surface of the skin and/or mucous membranes reach their target cells. In a few instances, especially in the uterine mucosa, the virus can enter the target tissue directly through the transition zone between the glandular and squamous epithelium of the endocervix and ectocervix without causing mucosal tissue damage.

Viral antigens and host receptors interact specifically at the molecular level to allow the virus to enter undifferentiated epithelial cells. Four HSPG-specific binding sites with high lysine (K) content were found in L1 after structural analyses, which are necessary for productive infection. The initial binding between the L1 and the HSPG occurs after they are in the intraepithelial milieu. It's interesting to note that L1 proteins attach to HSPGs through their K278–K361 a polar site, which is present on the FG and HI surface loops of two nearby pentamers; non-specific binding also takes place with non–HSPG receptors [Laminin 332 (LN332)]. These binds trigger the initial L1 protein 3D conformational change that is cyclophilin B (CPB) dependent, freeing the N terminus of the L2 protein, making it vulnerable to the proteolytic activity of furin, a cellular protease also known as protein convertase. Following the proteolysis of L2, L1 interacts with HSPGs twice, using the K54-K356 and N57-K59/K442-K443 sites on the FG/HI/BC and BC/4 surface loops of two pentamers, respectively. This allows for additional 3D conformational rearrangements of L1 and L2, which have two important effects on subsequent infection: 1) loss of affinity of bonds involved in the first interaction, reinforcing the bonds on site The virus is

taken up by small vesicles through endocytosis and transported to the nucleus through the ER and the Golgi. There, a series of interactions and structural adjustments of the vesicles enable decapitation and release of the viral genome close to the nuclear membrane. Nuclear pores allow the episomal viral genome to enter the nucleus and start viral replication. Epithelial cell differentiation is necessary for HPV replication. Indeed, the virus ensures its persistence and reproduction by affecting undifferentiated basal cells. Consistently, the basal cells simultaneously assure viral protein synthesis by dedifferentiating, as shown in, assuring viral multiplication (latent or active) and therefore raising the risk of HPV infection and associated illnesses.

The L1 protein is therefore crucial to the infection process (viral entry). It has the ability to increase immunity against HPV by creating a large number of highly efficient and specific antibodies that identify HPV in the physiological media due to the presence of numerous surface epitopes. Although the general modes of HPV infection are the same, as was previously shown, the pattern of gene expression is still distinct, and variations in virulence caused by variations depending on L1 protein. Therefore, given the divergence, a suitable idea in the effort to eradicate HPV infection would be to produce vaccines tailored from L1 proteins for each location.

2.3.0 Wart

Human papillomavirus is responsible for warts, which are skin infections (HPV). Rough, skin-colored pimples develop on the skin as a result of the illness. It is simple to distribute the virus. If warts aren't treated, the majority of kinds will disappear on their own in a few months to several years.[42] Skin-related HPV infections, commonly referred to as "cutaneous" infections, are quite frequent. Warts are benign skin growths that can develop as a result of HPV infections on the skin (verrucae). Warts are brought on by the accelerated cell development of the skin's outer layer. Warts have been reported since the time of the Greeks, but the virus that causes them was not identified until 1907[144]. Children are most frequently affected by skin warts, which typically develop and go away on their own within a few weeks or months.

Skin warts that return frequently are rather typical. All HPVs are believed to be capable of infecting a limited number of skin stem cells and resulting in "latent" infections that last for a long time. Even while these latent infections may never fully disappear, immunological management is expected to prevent the emergence of symptoms like warts[145]. Because immunological control is HPV type-specific, an individual may develop resistance to one form of HPV while remaining vulnerable to others.

There are different types of warts depending on the affected body part. These include;

- Flat warts affect the face and forehead.
- Plantar warts appear on the soles of the feet.
- Genitals warts are formed on the penis, vagina, or rectum.
- Periungual and subungual warts are formed under or around fingernails and toenails.

2.3.1 Genital Warts

A genital wart is a tiny growth of skin on, near, or on the anus. Certain varieties of the human papillomavirus (HPV) are the sexually transmitted infections that cause genital warts (HPV) [43]. HPV comes in a variety of forms. While some create genital or cutaneous warts, they are not hazardous. Others have the ability to spread infections that can result in cancer of the mouth, throat, anus, cervix, or penis. Any area of the body that is subject to sexual contact, such as the vulva, vagina, cervix, or groin in women, or the penis, scrotum, thigh, or groin in men, can acquire genital warts. They protrude from the skin's surface and are often pink in color[44].

Anyone who has sex runs the risk of getting hurt. The risk is increased by multiple-partner sexual activity and unprotected sex. The risk is also increased by a compromised immune system[48]. The HPV strains that generate warts on other regions of the body, such as the hands, feet, or inner thighs, are typically different from those that cause genital warts[146]. There are numerous HPV strains that can result in genital warts, but types 6 and 11 account for around 90% of all occurrences. However, there are more than 40 different

strains of HPV that can spread through sex and infect the skin of the anus and genitals. Genital warts may result from these illnesses, but they also may go undetected[146]. The majority of genital HPV infections are asymptomatic and disappear within a few months[147] thanks to the immune system. Additionally, even if they do not exhibit overt symptoms of illness, individuals can still transmit the virus to others. Most people develop genital HPV infections at some point in their life, and about 10% of women are infected right now. The likelihood of genital HPV infection increases dramatically as people get older and start having sexual relations. Similar to cutaneous HPV immunity, genital HPV immunity is assumed to be strain-specific[147].

2.3.2 External Genital Warts

External genital warts (EGWs) are sexually transmitted benign epidermal growths caused by the human papillomavirus (HPV), on the anogenital areas of both females and males. External genital warts (EGWs) are visible warts present on the external genital area. They may occur as one or more discrete lesions or coalesce into confluent plaques[45].

Warts are more common in people with impaired immune systems, but, in people with adequate immune function, about one-third may resolve spontaneously. Although more than 100 types of HPV have been identified, about one-third of which are found in the anogenital regions, most EGWs in immune-competent people are caused by HPV types 6 and 11[47]. External genital warts (EGWs) are visible warts that occur in the perinatal and perianal regions. They are due primarily to non-oncogenic human papillomavirus (HPV) types, usually types 6 and 11. Physical examination assisted by bright light and magnification is the recommended approach for primary diagnosis. A biopsy is indicated when EGWs are fixed to underlying structures or discoloured or when standard therapies are not effective. Recurrences are common, and there is no single treatment that is superior to others. Among women with atypical squamous cells, molecular HPV testing may be useful in determining who should be referred for colposcopy. Condoms may provide some protection against HPV-related diseases and thus are

recommended in new sexual relationships and when partnerships are not mutually monogamous. Because the efficacy of cesarean section in preventing vertical transmission of HPV infection from women with EGWs to their progeny has not been proved, it is not recommended. Common treatments for genital warts include patient- or clinician-applied topical therapies, as well as surgical and destructive approaches. Effectiveness varies among treatments, and head-to-head studies of all available modalities are lacking. Recurrence rates range from 25% to 67%. Patients with asymptomatic lesions may prefer no treatment, and one-third of cases clear spontaneously. Patient-applied treatments include imiquimod (Aldara), podofilox (Condylox), and sinecatechins (Veregen). Clinician-applied methods include podophyllin, trichloroacetic and bichloroacetic acids, cryotherapy, electrosurgery, and surgical excision.

Cellular immunity plays a role in how well EGWs are cleared from the body and remain there. In immune-competent individuals, the prognosis for clearing the wart and preventing recurrence is favorable; however, those with reduced cellular immunity (such as those with HIV or AIDS) have significant difficulties clearing the wart and keeping it clean. Without treatment, EGWs could get bigger, get more numerous, or stay the same size. About one-third would go away. [50] A sexually transmitted infection known as genital warts is brought on by specific forms of the human papillomavirus (HPV). They protrude from the skin's surface and are often pink in color. They typically don't cause many symptoms, however they can occasionally hurt. They typically start to show up one to eight months after exposure. The most noticeable sign of genital HPV infection is warts[50].

The majority of genital warts are caused by HPV types 6 and 11, but HPV types 16, 18, 31, 33, and 35 are also infrequently discovered. Direct skin-to-skin contact, typically during oral, genital, or anal sex with an infected partner, is how HIV is transmitted. Symptoms are typically used to make a diagnosis, and a biopsy can confirm it. The HPV strains that result in warts and cancer are not the same.

Both condoms and some HPV vaccines can help prevent genital warts. Creams like podophyllin, imiquimod, and trichloroacetic acid are among the treatment choices. Other options include surgery or

cryotherapy. Warts typically disappear within six months of treatment. Without therapy, they can resolve on their own in up to one-third of instances.

In the United States, 1% of the population has genital warts. But many people have the infection and show no signs of it. Without vaccination, almost everyone who engages in sexual activity will develop an HPV infection at some point in their lives. Since Hippocrates, who lived in 300 BC, the condition has at least been known about. The main method of HPV transmission is penetration intercourse. Although HPV can also be spread through non-penetrative sex, this method of transmission is less effective than penetrative sex. Concerning the impact of condoms on the spread of low-risk HPV, there is conflicting research. According to several research, they can effectively lower transmission. According to other studies, condoms are ineffective at preventing the spread of the low-risk HPV varieties that result in genital warts. There is some evidence that condoms are more successful at preventing infection in males than in females, suggesting that the impact of condoms on HPV transmission may differ depending on sex[49,50].

The HPV strains that result in warts are very contagious. Within eight months, warts appear on about three out of four unaffected partners of individuals who have them. HPV concordance rates are higher in couples where one spouse has visible warts, according to other studies of partner concordance, which raises the possibility that the presence of visible warts may be a sign of enhanced infectivity. The majority of the time, genital warts can be diagnosed visually, but occasionally a biopsy is necessary for confirmation. Molluscum contagiosum and smaller warts can occasionally be mistaken for one another. Histopathological, genital warts typically show nuclear alterations typical of HPV infections, parakeratosis, and rise above the skin's surface due to expansion of the dermal papillae (nuclear enlargement with perinuclear clearing). High-risk HPV infections can be diagnosed using DNA assays. DNA tests cannot be used to diagnose genital warts or other low-risk HPV infections since they are brought on by low-risk HPV strains.

Smaller warts are sometimes detected using an acetic acid solution (referred to as "subclinical lesions"), however this method is debatable. A 2007 UK guideline advises against its usage because a diagnosis obtained with acetic acid would not significantly alter the course of the disease and cannot be confirmed by a more specific test. HPV has no known treatment. Current therapies concentrate on getting rid of visible warts, however they can potentially go away on their own without any help. There is no proof that getting rid of visible warts slows down the spread of the underlying HPV infection. Up to 80% of HPV-positive individuals will recover from the infection in about 18 months.

Depending on the quantity, type, location, size, and other characteristics of the warts, a healthcare professional may suggest one of numerous treatment options. All medical procedures have the risk of depigmentation, itchiness, discomfort, or scarring.

Topical drugs or physically ablative treatments fall within this category. Physically ablative methods are thought to be more successful at removing warts for the first time, although they all have high recurrence rates.

Genital warts have been treated with a variety of methods, some of which have little scientific support for their efficacy or safety, including folk cures. The items in this list are those that are cited as having some basis in evidence for their usage in national or international practice recommendations. In the US, the prevalence of genital HPV infections is believed to be between 10 and 20 percent, with clinical symptoms occurring in 1% of sexually active adult population. Between 1975 and 2006, the prevalence of HPV infection increased in the US. The age range of the afflicted population, which is roughly 80%, is between 17 and 33. and Although therapies can get rid of warts, they don't get rid of the HPV, therefore warts can come back after treatment (around 50–73%). Additionally, warts may naturally recede (with or without treatment).

The virus was thought to stay in the body for a lifetime according to conventional wisdom. However, research utilizing sensitive DNA methods has demonstrated that the virus can either be eliminated or lowered to levels below those detected by polymerase chain reaction (PCR) testing by an immune

response. One investigation employing PCR to check genital skin for subclinical HPV discovered a 10% prevalence[50,51].

2.3.3 History of Genital Wart

Ciuffo used cell-free transmission tests to firmly confirm the virus's infectious nature in 1907. Genital warts were previously thought to be cutaneous symptoms of syphilis or gonorrhoea. Ciuffo produced novel papillomatous eruptions at the injection locations by inoculating and injecting wart extracts into previously uninfected skin[46]. Genital warts were discovered to be a benign cellular proliferation of the anogenital skin and mucosa in response to a viral invasion through further inquiry and experimentation. The virus, HPV, has been successfully identified as the source of genital wart epidemics[47].

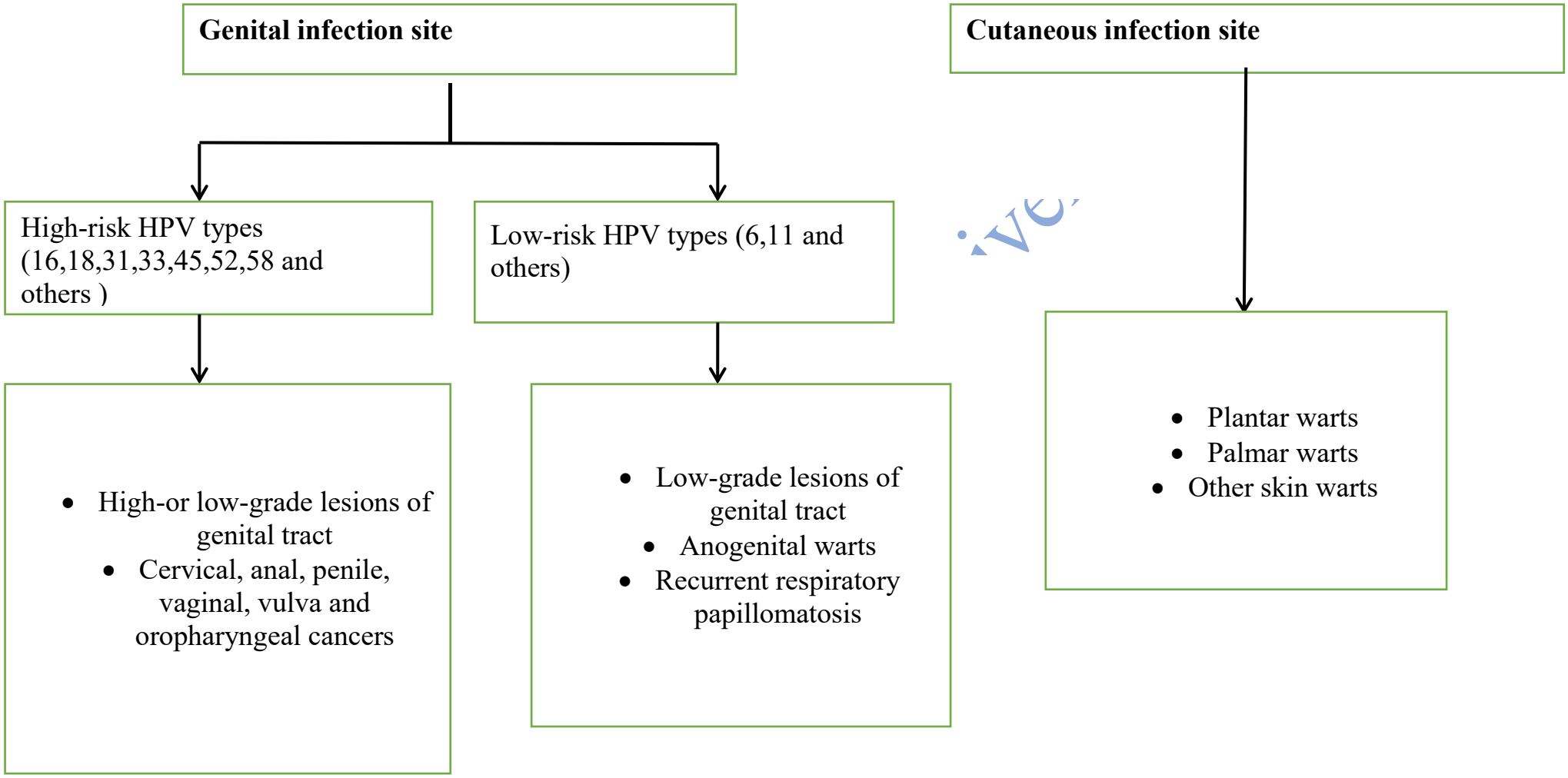


Figure 2.1: Human Papillomavirus Types and Disease Association

Source: (Donà et al. 2016)

2.4 Burden of the Disease Caused by HPV

More than 99% of cervical cancers are linked to HPV[51]. HPV16 and HPV18 are the most prevalent types, being found in more than 70% of samples from cervical cancer around the world[52]. In developing countries, cervical cancer is the most common cause of cancer death among women. Because 80% of cervical cancer deaths occur in nations with little resources, the disease burden contributes to global health disparity[53].

In addition to cervical cancer, HPV has been related to anogenital and oropharyngeal cancers in both men and women[51]. According to the International Agency for Research on Cancer (IARC) cervical cancer is caused entirely by HPV, other sexually transmitted cancers are caused by HPV to an erratic extent; penis 40%, anus 90%, vulva/vagina 40% and oropharynx 12% (9). HPV16 and HPV18 (particularly HPV16) account for an even larger proportion of the non-cervical HPV-associated cancers[54].

2.4.1 HPV Genotype Distribution and Prevalence

HPV genotypic prevalence varies by geographical region, despite the fact that the diseases brought on by HPV infection are the same everywhere regardless of the viral type (HR-HPV or LR-HPV, genital or cutaneous HPV)[10,52]. Policymakers can enhance vaccination programs in those areas or, to a lesser extent, develop a new generation of broad-spectrum vaccines with the aid of knowing the genotypic prevalence in a particular continental region. Strengthening vaccination campaigns or choosing vaccines based on the most prevalent genotypes will help to lower the socioeconomic and health costs of HPV infection. There are some HPV genotypes that are widespread worldwide. Numerous studies have found that HR-HPVs are the most prevalent types, with the most prevalent genotypes being 16, 18, 59, 45, 31, 33, 52, 58, 35, 39, 51, 56, and 53 in decreasing order of prevalence. The most prevalent LR-HPVs are HPV 6 and HPV 11, which cause almost all GWs. But where they are more common varies by area[55].

In conclusion, HPV 16 and 18 are less prevalent in developing countries where the burden of HPV-associated disease is higher than it is in developed countries, in contrast to the HPV global distribution

previously described. To understand this contradictory fact, keep in mind that the geographic variability of viral variants described later also affects the likelihood of CIN 1/2/3 and CC occurrence. African variants of HPV 16, 18, 33, and 45 are more virulent than other variants of HPV. Furthermore, due to a higher proportion of immunocompromised individuals, a lack of access to healthcare, and the ineffectiveness of vaccination programs, HR-HPVs are more prevalent in developing countries. For instance, the high-risk genotype HPV 66 has a slightly higher prevalence in developing nations, particularly in Africa in the case of CC. Genotypes 6 and 11, which are uncommon in Asia and Africa, are the most prevalent LR-HPVs in North America and, to a lesser extent, Europe. For instance, HPV 6 and 11 prevalence and incidence are low in Africa. It's interesting to note that several LR-HPVs, including HPV 26, 34, 61, 62, 83, and 84, that have been found in other parts of the world have not yet been discovered in Africa. Similar to HR-HPVs, low-risk African variants of HPV (primarily HPV 6 and 11) would have the highest virulence. Otherwise, unfavorable living conditions, subpar hygiene, a high prevalence of some infections (HIV, Chlamydia), which impair immune function (41), as well as a higher prevalence of other HR-HPVs (HPV51 and 52), may be to blame for the exclusive presence of some LR-HPVs in Africa (HPV 44, 70, 74 with 11% prevalence), which results in HPV-associated diseases (GW) and their burdens. The HPV population in Northern America is the least genotypically diverse, whereas Asia has a higher diversity.

2.4.2 Global Burden of HPV

The human papillomavirus (HPV) is a current public health concern. Infection with the human papillomavirus (HPV) has remained one of the most frequent viral infections around the globe[65]. In 2007, there were an estimated 291 million HPV-positive women in the world. HPV infections are still one of the most frequent viral illnesses around the globe[56]. In women without cervical abnormalities, the global prevalence of human papillomavirus (HPV) infection is 11-12%, with higher rates in Sub-Saharan Africa (24%), Eastern Europe (21 %), and Latin America (16 %) [55]. HPV16 and 18 (the two vaccine-preventable

strains) are responsible for more than 70% of all cervical cancer cases worldwide, with HPV16 and 18 accounting for 41% to 67% of high-grade cervical lesions and 16-32% of low-grade cervical lesions.

Following HPV16/18, the six most prevalent HPV types are the same throughout the world; these are HPV types 31, 33, 35, 45, 52, and 58; they cause an additional 20% of cervical cancers globally. 62 The most prevalent sexually transmitted infection in the US is reportedly HPV148. Most sexually active men and women will almost certainly develop genital HPV infections at some point in their lives. The American Social Health Association estimates that between 75 and 80 percent of Americans who engage in sexual activity will develop HPV at some point in their lives. By the time they turn 50, more than 80% of American women will have been exposed to at least one genital HPV strain. The number of new HPV infections among Americans aged 15 to 44 was estimated to be 6.2 million in 2000, with 74% of these infections occurring in those between the ages of 15 and 24148. Genital HPV was the most frequently acquired STD among the STDs examined. According to estimates, 10% of people in the US have an active HPV infection, 4% have one that has caused cytological abnormalities, and 1% have developed genital warts as a result of their infection. Estimates of the prevalence of HPV range from 1% to more than 90%. The discrepancy can be attributed, in part, to the fact that some studies focus on women who currently have a detectable infection, while others focus on women who have previously had a detectable infection. Another explanation for the discrepancy is the variation in strains tested. One study found that between 2003 and 2004, 26.8% of females between the ages of 14 and 59 had at least one type of HPV149. This was higher than earlier predictions, with 15.2% of cases containing at least one cancer-causing high-risk type. High-risk and low-risk types are about equally prevalent over time. The human papillomavirus is not one of the illnesses that are typically reportable to the CDC as of 2011150. Infection with HPV has a high prevalence worldwide, especially in women, where it is the main cause of cancer, making it a current public health priority. As one of the most widespread viral infections in the world, HPV infection was estimated to affect 291 million women globally in 2007. According to earlier studies, the prevalence of HPV among women with normal cervical cytology (NCC)

was 10.4% and 11.7 percent in 2007 and 2010, respectively. These numbers have been adjusted to 9.9% in 2019. Oceania (21.8%, estimated to be 30.9% in 2019) and Africa (21.1%) had the highest HPV prevalence among these women, followed by Europe (14.2%), America (11.5%), and Asia (11.5%). (9.4 percent). In 2011, 32.1 percent of 576,281 gynecologically healthy and unhealthy women in the general female population were HPV carriers. Asia and Africa had the highest prevalences, at 45.5 and 29.6 percent, respectively. Oceania has no data that are currently available. The significant intra-continental variation in HPV prevalence permits global regional repartition.

The HPV distribution profile in women with NCC is essentially the same as that of the general female population in terms of geographic world regions. In developing areas, it is higher. HPV prevalence was higher in Sub-Saharan Africa (SSA) (24.0%), particularly in the regions of Eastern Africa (33.6%) and Latin America, according to the studies compiled from cytologically healthy women. With regard to all females, Asian regions had the highest prevalence, with nearly half of Eastern, Central, and Southern Asians (57.7 and 44.4 percent, respectively) being carriers. In the SSA region, 42.2 and 32.3 percent of women in Southern and Eastern Africa were HPV carriers, respectively. Similar to Western Europe, almost all of Europe had low HPV prevalence (30%). (3.7 percent). As a result, developing regions (42.2%) have higher HPV infection rates than developed regions (22.6 percent). Regardless of development, the prevalence is relatively high in Eastern Europe (21.4%) and low in North Africa (9.2%) and Western Asia (2.2%). Additionally, age-related trends were consistent across all of these studies that included female participants. However, there was a resurgence of HPV infection in adults over 45 in the African (East and West Africa) and American (Central and Southern America) regions. Adolescent girls and women under the age of 25 were the most infected. Global prevalence rates of genital HPV infection in men range from 3.5 to 45 percent vs. 2 to 44 percent, and transmission rates are comparable. Given that most anogenital HPV infections are sexually transmitted, this is completely understandable. In fact, a 2014 study found that 9.0 percent of 4,065 healthy men from Europe, America, Asia, and Africa carried the HPV virus. When compared to heterosexual men, who are at risk of HPV infection

based on the number of sexual partners, homosexuals and men who are HIV-positive are at higher risk, with incidence rates of HPV anal infection higher (90%). In addition, the prevalence of HPV infection is the same for all men, regardless of age, and barely varies over time. Compared to earlier trends in women, this one is new. According to geographical distribution, men's HPV infection rates are higher in Africa, particularly among South African men (17.2 percent annually), and lower in Asia (3.2 percent per year). The prevalence of all HPV genotypes is higher in low- and middle-income countries compared to developed regions, according to research results by Giuliano et al.

Together, these data support the finding that HPV incidence and prevalence are most pronounced in low- and middle-income areas among healthy and unhealthy individuals of both sexes[19]. It is well known that HPV and other sexually transmitted infections are primarily spread by poverty and idleness. Additionally, given that the majority of women begin having relationships early, this is a plausible explanation for the extremely high prevalence rates of high-risk oncogenic genital HPVs (HR-HPVs) found in young women, particularly in low- and middle-income countries[36]. Interestingly, cultural diversity patterns, early marriages, and high divorce rates are important contributors to the spread of viruses in some underdeveloped regions, including SSA, East, and Southwest Asia. In addition, access to screening and healthcare in SSA continues to be difficult compared to developed nations, especially for women who marry very young (10–14 years old), which results in a lack of health empowerment. Some women typically clear the infection very quickly because of their strong immune systems, sexual stability, and financial security, which accounts for the drop in HPV prevalence after age 25. Older women exhibit low rates of persistence, recrudescence, or reinfection, which are typically brought on by multi-sexual relationships that result from social and economic instability (poverty) and illiteracy[34,51,52,54].

Second, in just 3 years (from 2007 to 2010), women with NCC experienced an increase in the overall prevalence of HPV infection of about 1% (10.4-11.7 percent, respectively), following the same pattern

as that seen in the various sub-continents previously mentioned. According to these findings, if the current vaccination program is not expanded or improved, the number of healthy HPV-positive women could rise by about 5% by 2025 (to about 17%), particularly in low- and middle-income nations. Despite the fact that the burden is lower in men, the increasing rate will be the same due to the dynamics of transmission. It is important to note that men are not necessarily poor carriers of the virus even though their HPV burden is lower than that of women[50]. In fact, studies conducted by Wei et al. refute the claim made by Beachler et al. that men have a lower HPV clearance rate. However, it is realistic to admit that men have a low clearance rate because they are less likely to develop natural anti-HPV immunity compared with women who clear the infection within a relatively shorter period than men, who clear the infection within a relatively shorter period than men given the large number of samples obtained from 18 countries combined (>24,000 participants) and a relatively long period of observation (1950-2015) in this study. Men's preferential sexual activity with young girls under 25 who are highly infected and the fact that men have a lower potential for developing natural or acquired immunity than women, even after repeated exposures, could both contribute to the high prevalence of HPV in men, which is age-invariable. This suggests that men serve as reservoirs or vector-based niches for HPVs (especially HR-HPVs) in women and MSM, where any sexual behavior is a potential method of transmission. This statement leads us to surmise that the 1% increase in infection rates seen in women may also occur in men[36].

2.4.3 Burden of HPV in Africa

HPV prevalence in Africa was reported to range between 7% and 60% worldwide, without taking cytologic findings into account[57]. In Sub-Saharan Africa, Bruni et al. (2010) found an HPV prevalence of 24% in women with normal cytology[58]. Because of variances in various parameters, such as bifacial solar, research populations, sexual behaviours, and HPV testing procedures, prevalence can vary between studies.

Ali-Risasi et al. (2008) discovered 98.2% HPV positivity in a group of 55 patients with dysplastic lesions of the uterine cervix, including (85.5%) HIV-positive patients. Immunodeficiency is well documented for allowing HPV infection to remain and spread[59]. Another study in Kinshasa found that 12.5% of women aged 30 and up had HPV. The difference in age of inclusion could explain the low prevalence rate[60].

In North Africa, the total HPV prevalence in a study of 391 women aged 18 to 65 was found to be 13.2%.[61] The prevalence would be expected to be greater in this study. One reason for this finding is the influence of cultural and sexual behaviours, which could act as protective factors by lowering the incidence of HPV infection among women in that group.

2.4.4 Burden of HPV in Nigeria

Nigeria has a population of 50.33 million women aged 15 and older who are at risk of cervical cancer, according to the ICO/IARC HPV Information Centre[63]. According to current statistics, 14943 women are diagnosed with cervical cancer each year, with 10403 dying from the disease. Cervical cancer is the second most common disease among Nigerian women and the second most common cancer among women aged 15 to 44. Cervical HPV-16/18 infection is predicted to affect 3.5% of women in the general population at any given time, and HPVs 16 and 18 are responsible for 66.9% of invasive cervical cancers[64].

2.5 HPV Infection's Pathophysiology, Evolution, and Natural History: Disease Risk Occurrence

The majority of sexually transmitted infections are HPV infections. Men and women can both be asymptomatic carriers, transmitters, and victims of HPV infection at the same time, making them both a part of the virus's epidemiological chain[65]. In this way, a person's sexual behavior and the risk factors for HPV infection are intricately linked. The most important ones are: getting involved in sexual relationships early in life, having a lot of sexual partners, and engaging in sexual activity with high-risk individuals like prostitutes and partners who have several sexual partners. Although it will only stop the

risk of transmission between sexual partners, male circumcision and routine condom usage can lower the risk of HPV transmission[66-68].

The groups with a high prevalence of HIV infection and prostitution-related women include those groupings. The cervix (transformation zone) and the pectineal line of the anal canal are the two organs most vulnerable to infection during the transmission, which primarily occurs through sexual contact. The cervix, vagina, and vulva in women, the glans, prepuce, and skin of the penis and scrotum in men, and the anal canal and perianal area in both women and men, are common sites where HPV DNA can be found.

All of these well-known indicators of progression include the viral type, the length of the infection over time, and, most likely, the viral load per cellular unit. HIV infection poses a risk for both infection and the emergence of neoplasms, particularly when immunosuppression is present. Smoking, having a large family, and using oral contraceptives long-term have also been identified as progression factors[69,70]. Possible contributing factors include diet, particularly one lacking in fruits and vegetables, and co-infection with other STDs like Chlamydia trachomatis and HSV-2[71–72.].

Both oncogenic and non-oncogenic strains of cervical HPV took 9.4 months to clear in women and 7.5 months to clear in men[73,74].

The median time to wart development after an incidental HPV 6 or 11 infection was 6 to 10 months (range up to 18 months). This is longer than the previously reported median period of 2.9 months for women who were infected with HPV type 6 or type 11[76].

Even in the absence of treatment, wart regression was common among women with human immunodeficiency virus (HIV)/AIDS and HIV-negative women: 60% of women with HIV/AIDS and 80% of HIV-negative women showed wart regression in the year following diagnosis.[77]

One of many large families of small viruses that are unique to their hosts, papillomaviruses are found in a wide range of animal species, including humans. There are 85 genotypes of the more than 200 types of human papillomavirus (HPV) that have been identified in humans. Harald Zur Hausen made the discovery that there is a connection between HPV and cervical cancer in the 1980s; this work earned him the 2008 Nobel Prize in Physiology or Medicine. More information would continue to support the association between particular HPV genotypes and cervical cancer over the ensuing ten years. Currently, 14 HPV genotypes—known as the high-risk HPVs—have been linked to cancer; HPV 16 and 18 are responsible for 70% of cervical cancers and precancerous lesions. Fortunately, cancer is not always the result of the infection. Some women have these high-risk strains of the virus but show no symptoms. Their immune system might even completely rid them of the infection. However, the ongoing infection does result in health issues for other women.

Cervical cancer is the fourth most common cancer in women overall. Cervical cancer is thought to have caused 570,000 new cases of diagnosis in 2018, and it is responsible for 7.5% of all deaths among female cancer patients. The most common way to contract HPV is through sexual activity. Skin-to-skin contact, however, is also a recognized method of transmission. So it should come as no surprise that there is proof that HPV may also contribute to other cancers, such as rectal, vulval, vaginal, penile, and oropharyngeal cancers. The cancer associated with this viral infection that has received the most research to date is cervical cancer. This is partly due to the accessibility of thorough screening techniques and the advancement of our knowledge of how specific HPV strains can cause carcinogenesis.

Basal epithelial cells divide asymmetrically to renew the basal layer and the cutaneous or mucosal epithelium during a typical cell cycle. As a result, the development of the apical epithelium continues to be the limit of the number of divisions during cell differentiation. Contrarily, HR-HPV infection promotes the continuation of this cell division, which serves as the long-term genesis of the previously

discussed HPV-related diseases. The hyperexpression of the E6 and E7 proteins, which occurs at the molecular level, is what keeps cell division from ceasing. Studies have demonstrated that the integration of the viral genome into the host genome results in the loss of expression of some viral genome parts, including E2, which negatively regulates p97, leading to the overexpression of the oncoproteins E6 and E7. The expression of E6 and E7 is freely induced by p97 in the absence of E2 repression activity, which compromises the molecular consequences and raises the risk of diseases, particularly cancers linked to HPV.

Clinically speaking, following a primary infection, the symptoms of the infection are not immediately apparent; as a result, acute HPV infection is very poorly documented. Because the prodromes associated with HPV acute infection occur very late after infection, the anti-HPV antibody kinetics have not yet been established; however, studies are in progress. Additionally, according to the information that is currently available, 98 percent of women are exposed to HPV infection, and between 30 and 40 percent of them are susceptible to infection. Fortunately, both genders experience temporary HPV infection in 75–90% of cases. Long-term manifestations of this infection include GW, CW, and low-grade CIN1 (cervical intraepithelial neoplasia) in women and PIN1 (penile intraepithelial neoplasia) in men. The HPV type or viral load, immune prowess, and anatomical site of infection all affect how long the virus remains inactive (2.5 years). A low risk of CIN (1.5%) exists in females who experience viral clearance and have normal cervical cytology. Viral reactivation in the case of viral latency results in the persistence of infection marked by the presence of CIN-PIN2/3, which can very rarely evolve (10% precisely 3.3%) to the development of ICC, as previously described. According to reports, immune weakened, abnormal cytology, intercourse, and persistence of HR-HPV infection are some of the major contributing factors to the development of ICC. It should be noted that reinfection after clearance, which presents a risk of developing CIN3 (3.4 percent) six times lower than the persistent infection due to acquired immunity, must be distinguished from the persistence of the infection. It is unknown if this statement refers to re-infections with the same strain of HPV as the original infection or with different

strains. However, we can speculate that the risk of developing CIN2/3 when reinfected is lower than that after persistence following a primo-infection due to the capsid proteins' capacity to induce the production of cross-reactive antibodies, as demonstrated in VLP studies. The E6 and E7 proteins are responsible for maintaining replication after infection has been established, with HPV L1 protein's main function being repeated cell-to-cell binding. By limiting the spread of the infection to other cells or by concentrating primarily on the naive population (children), who are not LR-HPV carriers, the modification of the natural history in terms of the reduction in infection rate could be accomplished

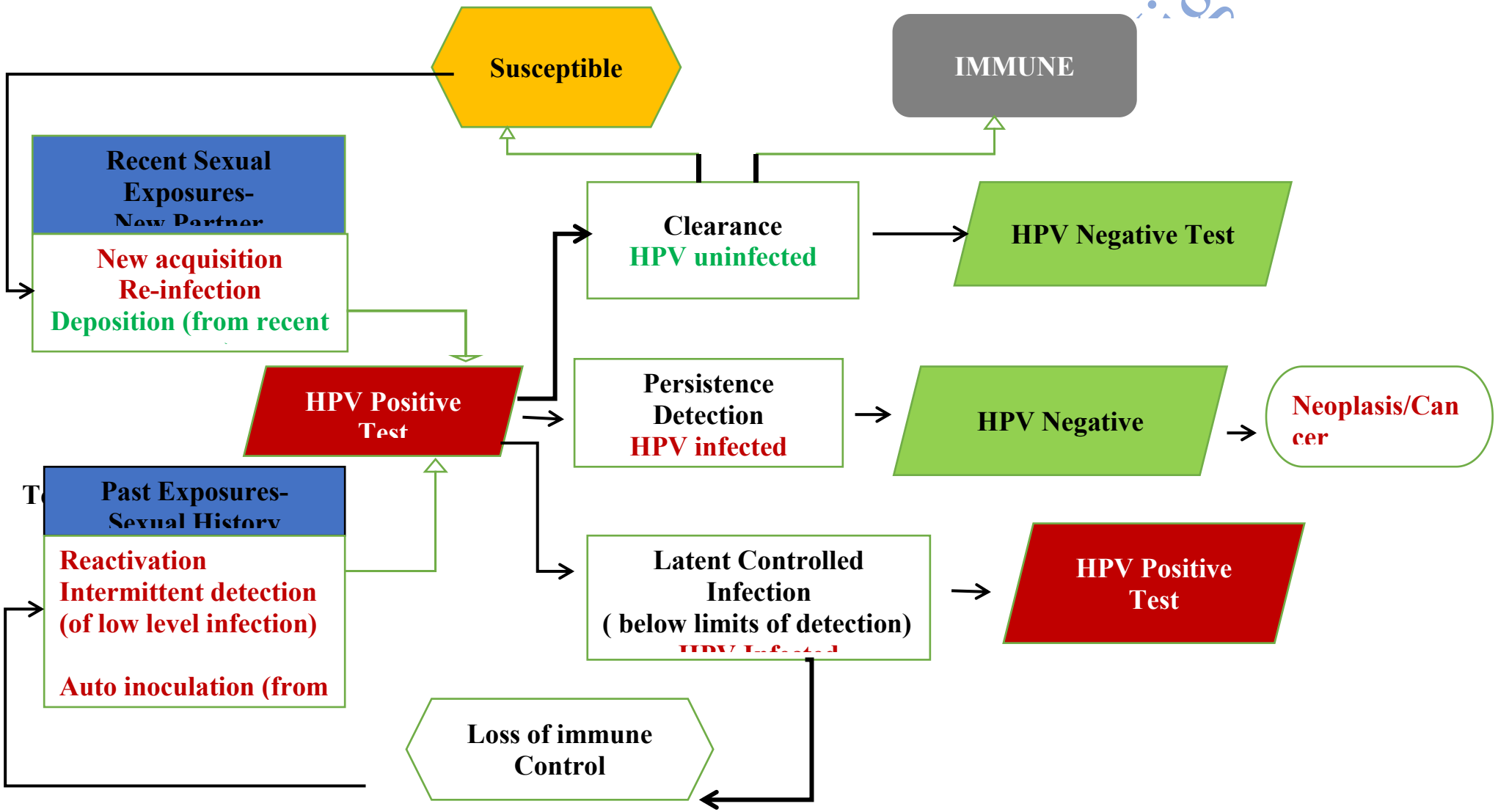


Figure 3.1: Schematic model of the individual-level natural history of female genital HPV infection across the life span

Source: Gravitt and Winer 2017

2.6 The Emergence of Cytological Evaluation

Between an infection and the emergence of cervical cancer or precancerous lesions, there is a protracted latency period. This prompted medical professionals to consider the question, "Would it be possible to detect infection early and treat the patient preventively to reduce the chance of danger?" DDrGeorgios Papanicolaou discovered that when cells taken from a woman's cervix were examined under a microscope, aberrations in cellular morphology could be seen. In Tennessee, the first widespread screening program was started in 1952. Since then, estimates suggest that between 105,000 and 492,000 instances of cervical cancer have been effectively avoided in the US over the previous three decades thanks to the Pap smear test. While a pathologist may be able to infer the presence of HPV through cytological analysis based on morphological abnormalities, diagnosis is largely dependent on molecular biology techniques, which enable identification of the HPV strain(s) and subsequent classification of the infection as high risk or low risk.

2.7 Nucleic Acid Hybridization Methods

The development of molecular tools made it possible to identify HPV strains with a strong correlation to cervical cancer. To find HPV, early nucleic acid hybridization techniques used radioactive nucleic acid probes, including Southern blotting, in situ hybridization (ISH), and dot blot hybridization. These hybridization techniques all benefit from the complementarity of the bases in nucleic acids. It is feasible to denature the DNA inside of a cell by using high temperatures and detergents, insert radiolabeled DNA probes, and then renaturate the probe to the native DNA strands by slowly cooling the cell. However, these procedures took a lot of time, and radioactivity is bad for human health. So, the demand for quicker, non-radioactive techniques emerged.

2.7.1 First Nuclear-Free Testing Technique

In order to meet this need, the first non-radioactive ISH probe became available in the 1980s. It offered a method for identifying the presence of HPV DNA in situ that was secure, quicker, extremely sensitive, and precise. The fact that ISH is simple to use on tissues that have already been repaired and processed is one of its main benefits. It also enables you to examine the cells for any morphological abnormalities while simultaneously determining the location of HPV DNA in the cellular nuclei of your sample. Either DNA or RNA oligonucleotide probes can be used for ISH. The usage of RNA probes has a number of significant advantages over DNA, despite the fact that DNA probes have been the "gold standard" for the past 40 years. First, the efficient synthesis of many continuously labeled probes of homogeneous lengths is made possible by the simple in vitro transcription of RNA probes. These RNA probes are more sensitive because they create hybrids that are more stable with the target RNA or DNA.

2.7.2 Reaction of Polymerase Chain

The polymerase chain reaction (PCR) or reverse transcriptase PCR (RT-PCR), respectively, can be used to amplify and quantify low copy quantities of DNA or mRNA in frozen or paraffin-embedded tissue slices or cell suspensions. Then, tagged probes are used to identify amplified DNA. The HPV genotype may be determined using a variety of PCR-based techniques, which can then be used to determine the patient's treatment requirements. These methods are widely employed, very sensitive, and precise. Consensus primers are used in conventional PCR experiments to allow the simultaneous amplification of several HPV genotypes. These primers specifically target the HPV genome's homologously conserved sections, which are shared by the majority of strains. Following amplification, the individual genotypes can be determined using a variety of methods, including direct sequencing, linear probe assays, restriction fragment length polymorphism (RFLP) analyses, and primers that are unique to each genotype. However, PCR is not error-proof, and false-negative findings can happen, especially with samples that have a low viral copy number and are contaminated with various HPV genotypes.

In Vitro RNA-RNA Hybridization

Other approaches keep developing along with technology, which enhances our capacity to accurately identify and treat people infected with high-risk HPV strains. One of the two FDA-approved diagnostic tests in the US at the moment is an in vitro DNA-RNA hybridization technique. In this approach, the target HPV-DNA is hybridized to tagged RNA probes in solution as a non-radioactive form of signal amplification. The DNA-RNA hybrids that have developed in solution are subsequently captured by certain antibodies affixed to the well of a microtiter plate. The caught hybrids are then found using luminescence. The quantity of target DNA contained in the samples and the intensity of the emission are directly connected. Although this test cannot genotype specific HPV strains, it can distinguish between infections with high and low risk. Additionally, this test is totally automatable, lowering the possibility of human mistake during sample processing.

Monitoring mRNA Expression

HPV RNA has become an area of interest as a target for the molecular diagnosis of HPV infection. Rather than testing for the presence of viral genomes, assessing the level of viral mRNA expression measures the viral activity in the infected cells. This can be very useful when trying to assess the severity of the infection, particularly if the HPV strain is one of the 14 cancer-causing strains. PCR-based methods, including RT-PCR, could be used to measure the levels of mRNA expression[10]. Another emerging method uses flow cytometry to detect the presence of HPV mRNA in whole cells. It combines the in situ hybridization technology with flow cytometry analysis, whereby the probe does not emit a fluorescent signal unless it is bound to its target sequence. Using this technique, the overexpression of HPV oncogenes can be assessed, and a prediction can be made on the likelihood of cervical cancer progression.

2.8 Immune Response After HPV Infection

The average time from HPV infection to seroconversion is approximately 8–12 months, although immunological response varies by individual and HPV type. HPV infections are restricted to the epithelial

layer of the mucosa and do not induce a vigorous immune response[78]. After natural infection, 70–80% of women seroconvert; their antibody responses are typically slow to develop and of low titre and avidity[79]. However, in men there is little response to HPV infection, few men seroconvert, and even after seroconversion, the antibodies produced are not protective[80].

2.9 Summary of the Gap in Literature

It is possible that women will be less likely to participate in cervical cancer screening if they are required to submit a blood sample to a laboratory for HPV DNA testing if they have the option to take the test themselves, this is one of the gaps in the literatures as some researchers combined both HPV self-sampling and clinician-sampling. Some of the studies that were looked at did not address the typical issues that could improve the self-sampling experience and boost its acceptability. These concerns include pain, anxiety, and the capacity to self-sample in an accurate manner. In addition, very few data were collected on the qualitative and quantitative efficacy of the instructions included in the self-sampling kit, as well as the marketing messages that were employed to encourage individuals to perform self-sampling. In addition, as the bulk of the studies that were considered were of the cross-sectional type, the reviewers were unable to draw any conclusions on the possibility of a causal relationship.

Endnotes

29. Huang, Wen Bo, Jimmy Yu Wai Chan, and Da Lie Liu. 2017. "Human Papillomavirus and World Health Organization Type III Nasopharyngeal Carcinoma: Multicenter Study from an Endemic Area in Southern China." *Cancer* 124, no. 3 (October): 530–36. https://doi.org/10.1002/cncr.31031.

30. Beyer, Walter E.P., and Albert D.M.E. Osterhaus. 2020. "Bivalent AS04-Adjuvanted HPV Vaccine Provides Optimal Cancer Prevention for HPV Types Not Included in the Vaccine." *Vaccine* 38, no. 47 (November): 7414–16. https://doi.org/10.1016/j.vaccine.2020.09.015.

31. World Health Organization. 2022. "Cervical Cancer." Www.who.int. February 22, 2022. https://www.who.int/news-room/fact-sheets/detail/cervical-cancer.

32. Shah, Khushali, Hiral Hapani, Anjana V. Trivedi, and Chetna K. Dodiya. 2020. "Role of CT Imaging in Oral Cavity and Oropharyngeal Squamous Cell Carcinoma." *International Journal of Contemporary Medicine, Surgery and Radiology* 5, no. 1 (March). https://doi.org/10.21276/ijcmsr.2020.5.1.23.

33. "Planned Parenthood." 2019. Plannedparenthood.org. 2019. https://www.plannedparenthood.org/learn/stds-hiv-safer-sex/hpv.

34. Guarner, Jeannette. 2019. "Introduction: One Health and Emerging Infectious Diseases." *Seminars in Diagnostic Pathology* 36, no. 3 (May): 143–45. https://doi.org/10.1053/j.semdp.2019.04.004.

35. "Planned Parenthood." 2019. Plannedparenthood.org. 2019. https://www.plannedparenthood.org/learn/birth-control/condom/how-effective-are-condoms.

36. Cancers Associated with Human Papillomavirus (HPV) | CDC." 2022. Www.cdc.gov. October 4,2022.https://www.cdc.gov/cancer/hpv/basic_info/cancers.htm#:~:text=caused%20by%20HPV.-

37. Aghaeipour, Farideh, Hamid Salehiniya, and Hamid Abbaszadeh. 2021. "Prevalence of Human Papillomavirus (HPV) in Oral Mucosal Lesions in Iran: A Systematic Review and Meta-Analysis." *Journal of Medical Virology*, June (June). https://doi.org/10.1002/jmv.27161.

38. Roik, Elena E., Ekaterina E. Sharashova, Evert Nieboer, Olga A. Kharkova, Vitaly A. Postoev, and Jon Ø Odland. 2017. "Knowledge about Human Papillomavirus and Prevention of Cervical Cancer among Women of Arkhangelsk, Northwest Russia." *PLoS ONE* 12, no. 12 (December): e0189534. https://doi.org/10.1371/journal.pone.0189534.

39. Kombe Kombe, Arnaud John, Bofeng Li, Ayesha Zahid, Hylemariam Mihiretie Mengist, Guy-Armel Bounda, Ying Zhou, and Tengchuan Jin. 2021. "Epidemiology and Burden of Human Papillomavirus and Related Diseases, Molecular Pathogenesis, and Vaccine Evaluation." *Frontiers in Public Health* 8, no. January (January). https://doi.org/10.3389/fpubh.2020.552028.

40. Akalın, Ayşe. 2022. "Human Papillomavirus (HPV) Enfeksiyonu ve HPV Aşısında Güncel Yaklaşımlar." *Androloji Bülteni*. https://doi.org/10.24898/tandro.2022.25993.

41. "Cervical Cancer Screening - Medical Information | BMJ Best Practice US." n.d. Bestpractice.bmj.com. Accessed October 7, 2022. https://bestpractice.bmj.com/topics/en-us/1123

42. Anonymous. 2017. "HPV and Genital Warts." Jo's Cervical Cancer Trust. September 18, 2017. https://www.jostrust.org.uk/information/hpv/hpv-and-genital-warts.

43. Abu, Selamawit Hirpa, Berhan Tassew Woldehanna, Etsehiwot Tilahun Nida, Abigiya Wondimagegnehu Tilahun, Mahlet Yigeremu Gebremariam, and Mitike Molla Sisay. 2020. "The Role of Health Education on Cervical Cancer Screening Uptake at Selected Health Centers in Addis Ababa." Edited by Stanley J. Robboy. *PLOS ONE* 15, no. 10 (October): e0239580. https://doi.org/10.1371/journal.pone.0239580.

44. Shah, Rajesh. 2021. "Preparation and Standardization of Human Papillomavirus (HPV) (Genotype 6) Nosode." *International Journal of High Dilution Research - ISSN 1982-6206* 18, no. 3-4 (April): 13–18. https://doi.org/10.51910/ijhdr.v18i3-4.965.

45. "Human Papillomavirus (HPV): Practice Essentials, Background, Pathophysiology." 2019. Medscape.com. October 19, 2019. https://emedicine.medscape.com/article/219110-overview.

46. Yuan, Jianwei, Guoying Ni, Tianfang Wang, Kate Mounsey, Shelley Cavezza, Xuan Pan, and Xiaosong Liu. 2018. "Genital Warts Treatment: Beyond Imiquimod." *Human Vaccines & Immunotherapeutics* 14, no. 7 (April): 1815–19. https://doi.org/10.1080/21645515.2018.1445947.

47. "Human Papillomavirus (HPV) Infection - STI Treatment Guidelines." 2021. Www.cdc.gov. August 18, 2021. https://www.cdc.gov/std/treatment-guidelines/anogenital-warts.htm.

48. "Imiquimod." 2020. *Reactions Weekly* 1786, no. 1 (January): 100–100. https://doi.org/10.1007/s40278-020-73574-z.

49. Dareng, Eileen O., Sally N. Adebamowo, Ayotunde Famooto, Oluwatoyosi Olawande, Michael K. Odutola, Yinka Olaniyan, Richard A. Offiong, Paul P. Pharoah, and Clement A. Adebamowo. 2019. "Prevalence and Incidence of Genital Warts and Cervical Human Papillomavirus Infections in Nigerian Women." *BMC Infectious Diseases* 19, no. 1 (January). https://doi.org/10.1186/s12879-018-3582-y.

50. Shoja, Zabihollah, Mohammad Farahmand, Neda Hosseini, and Somayeh Jalilvand. 2019. "A Meta-Analysis on Human Papillomavirus Type Distribution among Women with Cervical Neoplasia in the WHO Eastern Mediterranean Region." *Intervirology* 62, no. 3-4: 101–11. https://doi.org/10.1159/000502824.

51. Drolet, Mélanie, Jean-François Laprise, Dave Martin, Mark Jit, Élodie Bénard, Guillaume Gingras, Marie-Claude Boily, et al. 2021. "Optimal Human Papillomavirus Vaccination Strategies to Prevent Cervical Cancer in Low-Income and Middle-Income Countries in the Context of Limited Resources: A Mathematical Modelling Analysis." *The Lancet. Infectious Diseases* 21, no. 11 (November): 1598–1610. https://doi.org/10.1016/S1473-3099(20)30860-4.

52. "Oncology and Cancer Treatment." 2021. *International Journal of Cancer Research & Therapy* 6, no. 2 (May). https://doi.org/10.33140/ijcrt.06.02.01.

53. Venceslas Tarnju, Alemnju. 2021. "Global Burden of Cervical Cancer." *Cervical Cancer - a Global Public Health Treatise*, November (November). https://doi.org/10.5772/intechopen.98349.

54. Yuan, Xiao-wen, Yi-Jian Li, Quan Qiu, Zi-yuan Luo, and Xue-feng Zhao. 2019. "Prevalence and Genotype Distribution of Human Papillomavirus among 9945 Women from the Nanhai Area of Foshan." *BMC Infectious Diseases* 19, no. 1 (January). https://doi.org/10.1186/s12879-019-3687-y.

55. Xia, Xiaoyan, Dantong Shao, Huihui Liu, Mingxi Huang, Jia Yu, Jian-Rong He, and Xiu Qiu. 2022. "Age-Specific Prevalence of High-Risk Human Papillomavirus Infection among Women in Rural China, 2016–2018." *Journal of Infection*, July (July). https://doi.org/10.1016/j.jinf.2022.07.008.

56. "Estimating the Human Papillomavirus Genotype Attribution in Screen-Detected High-Grade Cervical Lesions." 2019. *Epidemiology*, October (October), 1. https://doi.org/10.1097/ede.0000000000001131

57. Kakar, Atul, Pooja Bakshi, Shikhar Tripathi, and Atul Gogia. 2022. "Anal Cytological Abnormalities in Human Immunodeficiency Virus-Infected Men and Prevalence of High-Risk Human

Papillomavirus Co-Infection." *Current Medicine Research and Practice* 12, no. 4: 152. https://doi.org/10.4103/cmrp.cmrp_114_21.

58. Ugrakli, Selin, Mehmet Ozdemir, Yasemin Derya Gulseren, and Sıddıka Fındık. 2021. "Prevalence and Genotype Distribution of High-Risk Human Papillomavirus Types Compared with Cervical Cytology." *Mediterranean Journal of Infection Microbes and Antimicrobials*, April (April). https://doi.org/10.4274/mjima.galenos.2021.2021.27.

59. Mutombo, Alex B., Ina Benoy, Rahma Tozin, Johannes Bogers, Jean-Pierre Van geertruyden, and Yves Jacquemyn. 2019. "Prevalence and Distribution of Human Papillomavirus Genotypes among Women in Kinshasa, the Democratic Republic of the Congo." *Journal of Global Oncology*, no. 5 (December): 1–9. https://doi.org/10.1200/jgo.19.00110.

60. Tornesello, Maria Lina, and Franco M. Buonaguro. 2020. "Human Papillomavirus and Cancers." *Cancers* 12, no. 12 (December): 3772. https://doi.org/10.3390/cancers12123772.

61. Williamson, Anna-Lise, Suzanne Garland, Joel Palefsky, Ed Rybicki, Margaret Stanley, and Silvia de Sanjosé. 2018. "The Cape Town Declaration on Human Papillomavirus Related Disease." *Papillomavirus Research* 5, no. June (June): 59–60. https://doi.org/10.1016/j.pvr.2017.12.003.

62. Zhang, Chanqiong, Chongan Huang, Xiang Zheng, and Dan Pan. 2018. "Prevalence of Human Papillomavirus among Wenzhou Women Diagnosed with Cervical Intraepithelial Neoplasia and Cervical Cancer." *Infectious Agents and Cancer* 13, no. 1 (November). https://doi.org/10.1186/s13027-018-0211-8.

63. Lall, Mahima, Sourav Sen, and Rajiv Mohan Gupta. 2019. "Human Immunodeficiency Virus and Human Papillomavirus in Immunopathology of Cervical Cancer." *International Journal of Contemporary Medical Research [IJCMR]* 6, no. 11 (November). https://doi.org/10.21276/ijcmr.2019.6.11.41.

64. Shapiro, Samantha B., Michel D. Wissing, Farzin Khosrow-Khavar, Mariam El-Zein, Ann N. Burchell, Pierre-Paul Tellier, François Coutlée, and Eduardo L. Franco. 2022. "Male Circumcision and Genital Human Papillomavirus (HPV) Infection in Males and Their Female Sexual Partners: Findings from the HPV Infection and Transmission among Couples through Heterosexual Activity (HITCH) Cohort Study." *The Journal of Infectious Diseases*, April (April). https://doi.org/10.1093/infdis/jiac147.

65. Campbell, Jean S., and Sara I. Pai. 2022. "Human Papillomavirus–Directed Therapeutics for Human Papillomavirus–Associated Oropharyngeal Cancer." *The Cancer Journal* 28, no. 5 (September): 407–15. https://doi.org/10.1097/ppo.0000000000000621.

66. Skorstengaard, Malene, Julie Suhr, and Elsebeth Lynge. 2019. "Condom Use to Enhance Regression of Cervical Intraepithelial Neoplasia: Study Protocol for a Randomized Controlled Trial." *Trials* 20, no. 1 (August). https://doi.org/10.1186/s13063-019-3564-4.

67. Reva, G.V., V.E. Tolmachev, Yu.V. Dynda, and A.R. Kim. 2021. "ROLE of HUMAN PAPILLOMAVIRUS in CARCINOGENESIS of DIGESTIVE TRACT." *European Journal of Natural History*, no. №1 2021: 33–37. https://doi.org/10.17513/ejnh.34146.

68. Mirabello, Lisa, Megan Clarke, Chase Nelson, Michael Dean, Nicolas Wentzensen, Meredith Yeager, Michael Cullen, Joseph Boland, Mark Schiffman, and Robert Burk. 2018. "The Intersection of HPV Epidemiology, Genomics and Mechanistic Studies of HPV-Mediated Carcinogenesis." *Viruses* 10, no. 2 (February): 80. https://doi.org/10.3390/v10020080.

69. Luvián-Morales, J., M. Delgadillo-González, L. Flores-Cisneros, L. Cetina-Pérez, and D. Castro-Eguiluz. 2021. "Effect of an Anti-Inflammatory Diet on Cervical Cancer Patients." *Clinical Nutrition ESPEN* 46, no. December (December): S710–11. https://doi.org/10.1016/j.clnesp.2021.09.472.

70. Kilic, Cigdem. 2021. "Association of Human Papillomavirus and Chlamydia Trachomatis Coinfection with Cervical Intraepithelial Lesions and Cervical Cancer." *Current Obstetrics and Gynecology Reports*, November (November). https://doi.org/10.1007/s13669-021-00319-y.

71. Suomenrinne-Nordvik, Anna, and Simopekka Vänskä. 2021. "The Confounding Effect of Multi-Type Human Papillomavirus Infections on Type-Specific Natural History Parameter Identification." *Epidemics* 36, no. September (September): 100468. https://doi.org/10.1016/j.epidem.2021.100468.

72. Chikandiwa, Admire, Pedro T. Pisa, Etienne E. Muller, Catherine Tamalet, Philippe Mayaud, Matthew F. Chersich, and Sinead Delany-Moretlwe. 2019. "Incidence, Persistence, Clearance, and Correlates of Genital Human Papillomavirus Infection and Anogenital Warts in a Cohort of Men Living with Human Immunodeficiency Virus in South Africa." *Sexually Transmitted Diseases* 46, no. 5 (May): 347–53. https://doi.org/10.1097/olq.0000000000000979.

73. "Incidence of HPV Infection and HPV-Associated Disease in Screening Indian Men Who Have Sex with HIV-Positive Men." 2019. *Case Medical Research*, October (October). https://doi.org/10.31525/ct1-nct04142398.

74. Liu, Jun, Mei Luo, Yang Zhang, Guangming Cao, and Shuzhen Wang. 2020. "Association of High-Risk Human Papillomavirus Infection Duration and Cervical Lesions with Vaginal Microbiota Composition." *Annals of Translational Medicine* 8, no. 18 (September): 1161–61. https://doi.org/10.21037/atm-20-5832.

75. Day, Tania, Alexandra Marzol, Ross Pagano, Ken Jaaback, and James Scurry. 2020. "Clinicopathologic Diagnosis of Differentiated Vulvar Intraepithelial Neoplasia and Vulvar Aberrant Maturation." *Journal of Lower Genital Tract Disease* 24, no. 4 (October): 392–98. https://doi.org/10.1097/lgt.0000000000000569.

76. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans: human papillomaviruses. Vol. 90. Lyon, IARC, 2007. Available at http://monographs.iarc.fr/ENG/Monographs/vol90/mono90.pdf, accessed August 2021

77. Ozbun, Michelle A. 2019. "Extracellular Events Impacting Human Papillomavirus Infections: Epithelial Wounding to Cell Signaling Involved in Virus Entry." *Papillomavirus Research* 7, no. June (June): 188–92. https://doi.org/10.1016/j.pvr.2019.04.009.

78. Chikandiwa, Admire, Pedro T. Pisa, Etienne E. Muller, Catherine Tamalet, Philippe Mayaud, Matthew F. Chersich, and Sinead Delany-Moretlwe. 2019. "Incidence, Persistence, Clearance, and Correlates of Genital Human Papillomavirus Infection and Anogenital Warts in a Cohort of Men Living with Human Immunodeficiency Virus in South Africa." *Sexually Transmitted Diseases* 46, no. 5 (May): 347–53. https://doi.org/10.1097/olq.0000000000000979.

79. Khasanov, Doniyorbek Shuxratbekovich, and Dilfuzahon Zakirzhanovna Mamarasulova. 2021. "Testing the Human Papillomavirus in the Primary Screening of the Cervical Disease." *ACADEMICIA: An International Multidisciplinary Research Journal* 11, no. 12: 766–69. https://doi.org/10.5958/2249-7137.2021.02740.3.

80. Eklund, Carina, Ola Forslund, Keng-Ling Wallin, and Joakim Dillner. 2018. "Continuing Global Improvement in Human Papillomavirus DNA Genotyping Services: The 2013 and 2014 HPV LabNet International Proficiency Studies." *Journal of Clinical Virology* 101, no. April (April): 74–85. https://doi.org/10.1016/j.jcv.2018.01.016.

81. Biazin, Habtamu. 2021. "Concordance of Anyplex™ II HPV HR Assays with Reference HPV Assays in Cervical Cancer Screening: Systematic Review." *Journal of Virological Methods*, December (December), 114435. https://doi.org/10.1016/j.jviromet.2021.114435

82. Saxena, Varsha, Vidya Pai, K Rajagopal, and Abdulla Mehnaz. 2018. "Molecular Detection of Human Papillomavirus (HPV) in Females and Assessment of Risk Factors for HPV Infection: A Study from Coastal Karnataka." *JOURNAL of CLINICAL and DIAGNOSTIC RESEARCH*. https://doi.org/10.7860/jcdr/2018/35457.11642.

83. Dasgupta, Shirin. 2022. "A Review on Cervical Dysplasia: Etiology, Risk Factors, Diagnostic Biomarkers and Possible Nutritional Association." *Asian Pacific Journal of Cancer Care* 7, no. 3 (August): 555–63. https://doi.org/10.31557/apjcc.2022.7.3.555-563.

84. Ugrakli, Selin, Mehmet Ozdemir, Yasemin Derya Gulseren, and Sıddıka Fındık. 2021. "Prevalence and Genotype Distribution of High-Risk Human Papillomavirus Types Compared with Cervical Cytology." *Mediterranean Journal of Infection Microbes and Antimicrobials*, April (April). https://doi.org/10.4274/mjima.galenos.2021.2021.27.

85. Kim, Jiae, and Cheulhee Jung. 2022. "SF-QPCR: Strand Displacement-Based Fast Quantitative Polymerase Chain Reaction." *BioChip Journal* 16, no. 1 (January): 41–48. https://doi.org/10.1007/s13206-021-00044-x.

86. Zucchetto, Antonella, Guglielmo Ronco, Paolo Giorgi Rossi, Stefano Ferretti, Marco Zappa, Franzo Antonella, Falcini Fabio, et al. 2012. "Abstract B06: Screening Patterns within Organized Programs of Italian Women with Invasive Cervical Cancer." *Cancer Prevention Research* 5, no. 11_Supplement (November): B06–6. https://doi.org/10.1158/1940-6207.prev-12-b06.

87. Arbyn, Marc, Sara B Smith, Sarah Temin, Farhana Sultana, and Philip Castle. 2018. "Detecting Cervical Precancer and Reaching Underscreened Women by Using HPV Testing on Self Samples: Updated Meta-Analyses." *BMJ*, December (December), k4823. https://doi.org/10.1136/bmj.k4823.

88. Harder, Elise, Kirsten E. Juul, Signe M. Jensen, Louise T. Thomsen, Kirsten Frederiksen, and Susanne K. Kjaer. 2018. "Factors Associated with Non-Participation in Cervical Cancer Screening – a Nationwide Study of Nearly Half a Million Women in Denmark." *Preventive Medicine* 111, no. June (June): 94–100. https://doi.org/10.1016/j.ypmed.2018.02.035.

89. Volgareva, G. M. 2020. "Papillomaviral Carcinogenesis. Major Achievements And Certain Challenges Part I. General Notions Of Papillomaviruses. Human Papillomaviruses-Associated Cancers." *Russian Journal of Biotherapy* 19, no. 1 (March): 6–12. https://doi.org/10.17650/1726-9784-2019-19-1-6-12.

90. Zhou, Lei. 2021. "Concerns about Human Papillomavirus-Associated Oropharyngeal Cancer Detection Methods." *Oral Oncology*, January (January), 105143. https://doi.org/10.1016/j.oraloncology.2020.105143.

91. "Tampon Derişiminin Biyosensör Cevabına Etkisi." 2019. *FUTURE BIOCHEMISTRY and BIOSCIENCE*, April (April), 8–11. https://doi.org/10.48086/asd005.

92. Murahwa, Alltalents T., Mqondisi Tshabalala, and Anna-Lise Williamson. 2020. "Recombination between High-Risk Human Papillomaviruses and Non-Human Primate Papillomaviruses: Evidence of Ancient Host Switching among Alphapapillomaviruses." *Journal of Molecular Evolution* 88, no. 5 (May): 453–62. https://doi.org/10.1007/s00239-020-09946-0.

93. Östensson, Ellinor, Karen Belkić, Torbjörn Ramqvist, Miriam Mints, and Sonia Andersson. 2021. "Self- Sampling for High- Risk Human Papillomavirus as a Follow- up Alternative after Treatment of High- Grade Cervical Intraepithelial Neoplasia." *Oncology Letters* 21, no. 4 (January). https://doi.org/10.3892/ol.2021.12501.

94. Esber, Allahna. 2018. "Feasibility, Validity and Acceptability of Self-Collected Samples for Human Papillomavirus (HPV) Testing in Rural Malawi." *Malawi Medical Journal* 30, no. 2 (June): 61. https://doi.org/10.4314/mmj.v30i2.2.

95. Stoler, M.H., T.C. Wright, Jr., and A. Sharma. 2021. "High-Risk Human Papillomavirus Testing in Women with ASCUS Cytology: Results from the ATHENA HPV Study." *Reproductive Endocrinology*, no. 57 (March): 93–98. https://doi.org/10.18370/2309-4117.2021.57.93-98.

96. Kellen, Eliane, Ina Benoy, Davy Vanden Broeck, Patrick Martens, Jean-Paul Bogers, Annemie Haelens, and Erik Van Limbergen. 2018. "A Randomized, Controlled Trial of Two Strategies of Offering the Home-Based HPV Self-Sampling Test to Non- Participants in the Flemish Cervical Cancer Screening Program." *International Journal of Cancer* 143, no. 4 (April): 861–68. https://doi.org/10.1002/ijc.31391.

97. Asjes, Caitlin, and Jeff Andrews. 2018. "The Potential Cost-Effectiveness of Extended Genotyping in US Cervical Cancer Screening Paradigms [14Q]." *Obstetrics & Gynecology* 131, no. May (May): 188S. https://doi.org/10.1097/01.aog.0000533227.52261.92.

98. Yan, Dong, Bai v, Zhang Yuping, Shang Guang Jie, Zhao Yan, and Dongfeng Tan. 2017. "Comparison of Three Screening Methods for Cervical Cancer in China - a Systematic Study of 3,300 Cases in Rural Areas of Shanxi Province." *Journal of Cytology & Histology* 08, no. 05. https://doi.org/10.4172/2157-7099.1000492.

99. Biederman, Erika, Victoria Champion, and Gregory Zimet. 2020. "A Conjoint Analysis Study on Self-Sampling for Human Papillomavirus (HPV) Testing Characteristics among Black Women in Indiana." *BMC Women's Health* 20, no. 1 (March). https://doi.org/10.1186/s12905-020-00921-x.

100. Stenvall H, Wikstrom I, Backlund I, and Wilander E. 2017. Accuracy of HPV testing of vaginal smear obtained with a novel self-sampling device. *Acta Obstet. Gynecol. Scand.* 86:16–21.Winer RL. 2017. Concordance of self-collected and clinician-collected swab samples for detecting human papillomavirus DNA in women 18 to 32 years of age. *Sex. Transm. Dis.* 34:371–377.

101. Schmeink CE, Bekkers RL, Massuger LF, and Melchers WJ. 2021. The potential role of self-sampling for high-risk human papillomavirus detection in cervical cancer screening. *Rev. Med. Virol.* 21:139–153.

102. Sellersllors JW. 2020. Comparison of self-collected vaginal, vulvar and urine samples with physician-collected cervical samples for human papillomavirus testing to detect high-grade squamous intraepithelial lesions. *CMAJ* 163:513–518.

103. Lenselink CH. 2019. Detection and genotyping of human papillomavirus in self-obtained cervicovaginal samples by using the FTA cartridge: new possibilities for cervical cancer screening. *J. Clin. Microbiol.* 47:2564–2570.

104. Ørnskov, Dorthe, Kirsten Jochumsen, Pernille Husted Steiner, Ivan Moulun Grunnet, Annemette Wildfang Lykkebo, and Marianne Waldstrøm. 2021. "Clinical Performance and Acceptability of Self-Collected Vaginal and Urine Samples Compared with Clinician-Taken Cervical Samples for HPV Testing among Women Referred for Colposcopy. A Cross-Sectional Study." *BMJ Open* 11, no. 3 (March): e041512. https://doi.org/10.1136/bmjopen-2020-041512.

105. CH. L. Aslesha et al., CH. L. Aslesha et al. 2020. "Detection of Nature of the Fabricated Material by Upset Forging, an Experimental and Simulation Study." *International Journal of Mechanical and Production Engineering Research and Development* 10, no. 3: 1663–70. https://doi.org/10.24247/ijmperdjun2020149.

106. Cai, Rentian, Li Liu, Bin Luo, Jiangrong Wang, Jiayin Shen, Yinzhong Shen, Renfang Zhang, Jun Chen, and Hongzhou Lu. 2017. "Caspase-1 Activity in CD4 T Cells Is Downregulated Following Antiretroviral Therapy for HIV-1 Infection." *AIDS Research and Human Retroviruses* 33, no. 2 (February): 164–71. https://doi.org/10.1089/aid.2016.0234.

107. Vidya Vijayan, K. K., Krithika Priyadarshini Karthigeyan, Srikanth P. Tripathi, and Luke Elizabeth Hanna. 2017. "Pathophysiology of CD4+ T-Cell Depletion in HIV-1 and HIV-2 Infections." *Frontiers in Immunology* 8, no. 580 (May). https://doi.org/10.3389/fimmu.2017.00580.

.

108. Kiros, Mulugeta, Demeke Mesfin Belay, Sisay Getu, Wasihun Hailemichael, Ahmed Esmael, Henok Andualem, and Alene Geteneh. 2021. "Prevalence and Determinants of Pre-Cancerous Cervical Lesion and Human Papillomavirus among HIV-Infected and HIV-Uninfected Women in North-West Ethiopia: A Comparative Retrospective Cross-Sectional Study." *HIV/AIDS - Research and Palliative Care* Volume 13, no. June (June): 719–25. https://doi.org/10.2147/hiv.s310905.

109. Jolly, Pauline E., Simangele Mthethwa-Hleta, Luz A. Padilla, Jessica Pettis, ShaCoria Winston, Tomi F. Akinyemiju, Hannah J. Turner, 2017. "Screening, Prevalence, and Risk Factors for Cervical Lesions among HIV Positive and HIV Negative Women in Swaziland." *BMC Public Health* 17, no. 1 (February). https://doi.org/10.1186/s12889-017-4120-3.

110. American Cancer Society. 2017. "What Is Cervical Cancer?" Cancer.org. American Cancer Society. 2017. https://www.cancer.org/cancer/cervical-cancer/about/what-is-cervical-cancer.html.

111. Nicol, C., L. Duska, P. Hornsby, A. Pannone, and R.G. Bernheim. 2018. "HPV Vaccination Rates and Attitudes: A Cross-Sectional Survey of College Men and Women." *Gynecologic Oncology* 141, no. June (June): 112. https://doi.org/10.1016/j.ygyno.2016.04.302.

112. Mayo Clinic. 2017. "Cervical Cancer - Symptoms and Causes." Mayo Clinic. 2017. https://www.mayoclinic.org/diseases-conditions/cervical-cancer/symptoms-causes/syc-20352501.

113. JH, Kastan MB, Tepper JE, eds. Abeloff's Clinical Oncology. 6th ed. Philadelphia, Pa:Elsevier; 2020.

114. Yeh, Ping Teresa, Caitlin E Kennedy, Hugo de Vuyst, and Manjulaa Narasimhan. 2019. "Self-Sampling for Human Papillomavirus (HPV) Testing: A Systematic Review and Meta-Analysis." *BMJ Global Health* 4, no. 3 (May): e001351. https://doi.org/10.1136/bmjgh-2018-001351.

115. Karnon, J., J. Peters, J. Platt, J. Chilcott, E. McGoogan, and N. Brewer. 2018. *Liquid-Based Cytology in Cervical Screening: An Updated Rapid and Systematic Review and Economic Analysis*. *Www.ncbi.nlm.nih.gov*. NIHR Journals Library. https://www.ncbi.nlm.nih.gov/books/NBK62300/.

116. Karnon, J., J. Peters, J. Platt, J. Chilcott, E. McGoogan, and N. Brewer. 2018. *Liquid-Based Cytology in Cervical Screening: An Updated Rapid and Systematic Review and Economic Analysis*. *Www.ncbi.nlm.nih.gov*. NIHR Journals Library. https://www.ncbi.nlm.nih.gov/books/NBK62300/.

117. Aggarwal, Pakhee. 2019. "Cervical Cancer: Can It Be Prevented?" *World Journal of Clinical Oncology* 5, no. 4: 775. https://doi.org/10.5306/wjco.v5.i4.775.

118. Bray, Freddie, Jacques Ferlay, Isabelle Soerjomataram, Rebecca L. Siegel, Lindsey A. Torre, and Ahmedin Jemal. 2018. "Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries." *CA: A Cancer Journal for Clinicians* 68, no. 6 (September): 394–424. https://doi.org/10.3322/caac.21492.

119. World Health Organization. 2022. "Cervical Cancer." Www.who.int. February 22, 2022. https://www.who.int/news-room/fact-sheets/detail/cervical-cancer.

120. "Cervical Cancer: Symptoms, Causes, Stages, and Treatment." 2021. Www.medicalnewstoday.com. September 27, 2021. https://www.medicalnewstoday.com/articles/what-you-need-to-know-about-cervical-cancer.

121. Ngcobo, Ntombenle, Anelisa Jaca, Chinwe Juliana Iwu-Jaja, and Edison Mavundza. 2021. "Reflection: Burden of Cervical Cancer in Sub-Saharan Africa and Progress with HPV Vaccination." *Current Opinion in Immunology* 71, no. August (August): 21–26. https://doi.org/10.1016/j.coi.2021.03.006.

122. Almehmadi, Mazen, Magdi Salih, and Ayman Al-hazmi. 2019. "Awareness of Human Papillomavirus Infection Complications, Cervical Cancer, and Vaccine among the Saudi Population. A Cross-Sectional Survey." *Saudi Medical Journal* 40, no. 6 (June): 555–59. https://doi.org/10.15537/smj.2019.6.24208.

123. National Cancer Institute. 2018. "Human Papillomavirus (HPV) Vaccines." National Cancer Institute. Cancer.gov. 2018. https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-vaccine-fact-sheet.

124. Cancer Research UK. 2017. "About Cervical Screening | Cervical Cancer | Cancer Research UK." Cancerresearchuk.org. 2017. https://www.cancerresearchuk.org/about-cancer/cervical-cancer/getting-diagnosed/screening/about.

125. Ogilvie, Gina, Carolyn Nakisige, Warner K. Huh, Ravi Mehrotra, Eduardo L. Franco, and Jose Jeronimo. 2017. "Optimizing Secondary Prevention of Cervical Cancer: Recent Advances and Future Challenges." *International Journal of Gynecology & Obstetrics* 138, no. July (July): 15–19. https://doi.org/10.1002/ijgo.12187.

126. Getinet, Mamaru, Molla Taye, Abebe Ayinalem, and Menberesibhat Gitie. 2021. "Precancerous Lesions of the Cervix and Associated Factors among Women of East Gojjam, Northwest Ethiopia, 2020." *Cancer Management and Research* Volume 13, no. December (December): 9401–10. https://doi.org/10.2147/cmar.s338177.

127. Karnon, J., J. Peters, J. Platt, J. Chilcott, E. McGoogan, and N. Brewer. 2019. *Liquid-Based Cytology in Cervical Screening: An Updated Rapid and Systematic Review and Economic Analysis*. *Www.ncbi.nlm.nih.gov*. NIHR Journals Library. https://www.ncbi.nlm.nih.gov/books/NBK62300/.

128. Burd, Eileen M. 2017. "Human Papillomavirus Detection and Utility of Testing." *Clinical Microbiology Newsletter* 29, no. 21 (November): 159–67. https://doi.org/10.1016/j.clinmicnews.2007.10.001.

129. Cancer.org. American Cancer Society. 2017. https://www.cancer.org/cancer/cervical-cancer/causes-risks-prevention/prevention.html.

142. Taberna, M., M. Mena, M. A. Pavón, L. Alemany, M. L. Gillison, and R. Mesía. 2017. "Human Papillomavirus-Related Oropharyngeal Cancer." *Annals of Oncology* 28, no. 10 (October): 2386–98. https://doi.org/10.1093/annonc/mdx304.

143. Brisson M, Kim JJ, Canfell K, Drolet M, Gingras G, Burger EA, Martin D, Simms KT, Bénard É, Boily MC, Sy S. Impact of HPV vaccination and cervical screening on cervical cancer elimination: comparative modelling analysis in 78 low-income and lower-middle-income countries. The Lancet. 2020 Feb 22;395(10224):575-90.

144. "Human Papillomavirus (HPV)." 2021. The Well Project. November 23, 2021. https://www.thewellproject.org/hiv-information/human-papillomavirus-hpv.

145. Doorbar, John. 2018. "Host Control of Human Papillomavirus Infection and Disease." *Best Practice & Research Clinical Obstetrics & Gynaecology* 47, no. February (February): 27–41. https://doi.org/10.1016/j.bpobgyn.2017.08.001.

146. Bilenchi, Roberta, Marco Campoli, Emanuele Trovato, Elisa Cinotti, Pietro Rubegni, and Michele Fimiani. 2018. "Sinecatechins 10% Ointment for Genital Warts: Case Report of a Beneficial Reaction in an HIV-Positive Woman." *International Journal of STD & AIDS* 29, no. 10 (April): 1033–35. https://doi.org/10.1177/0956462418763888.

.

147. Sanjose, Silvia de, Maria Brotons, D Scott LaMontagne, and Laia Bruni. 2019. "Human Papillomavirus Vaccine Disease Impact beyond Expectations." *Current Opinion in Virology* 39, no. December (December): 16–22. https://doi.org/10.1016/j.coviro.2019.06.006.

148. Han, Jasmine J., Thomas H. Beltran, John W. Song, John Klaric, and Y. Sammy Choi. 2017. "Prevalence of Genital Human Papillomavirus Infection and Human Papillomavirus Vaccination Rates among US Adult Men." *JAMA Oncology* 3, no. 6 (June): 810. https://doi.org/10.1001/jamaoncol.2016.6192.

149 Combita, Alba L., Viviana Reyes, Devi Puerto, Raúl Murillo, Ricardo Sánchez, Marcela Nuñez, Gustavo A. Hernandez-Suarez, and Carolina Wiesner. 2022. "Reduction in Vaccine HPV Type Infections in a Young Women Group (18–25 Years) Five Years after HPV Vaccine Introduction in Colombia." *Cancer Prevention Research* 15, no. 1 (January): 55–66. https://doi.org/10.1158/1940-6207.capr-21-0063.

[150] Luo, Li-pei, Ping He, Qiao-tu Liu, Yang-hua Jiang, Yang-nan Zhang, Qing-zhao Li, Qiu Li, et al. 2021. "Prevalence and Genotype Distribution of HPV Infection among 214,715 Women from Southern China, 2012–2018: Baseline Measures prior to Mass HPV Vaccination." *BMC Infectious Diseases* 21, no. 1 (April). https://doi.org/10.1186/s12879-021-06019-5.

151 Song, Dan, Hong Li, Haibo Li, and Jianrong Dai. 2015. "Effect of Human Papillomavirus Infection on the Immune System and Its Role in the Course of Cervical Cancer." *Oncology Letters* 10, no. 2 (May): 600–606. https://doi.org/10.3892/ol.2015.3295.

152 Gravitt, Patti, and Rachel Winer. 2017. "Natural History of HPV Infection across the Lifespan: Role of Viral Latency." *Viruses* 9, no. 10 (September): 267. https://doi.org/10.3390/v9100267.

153 Donà, Maria Gabriella, Tarik Gheit, Maria Fenicia Vescio, Alessandra Latini, Domenico Moretto, Maria Benevolo, Antonio Cristaudo, Massimo Tommasino, and Massimo Giuliani. 2016. "Incidence, Clearance and Duration of Cutaneous Beta and Gamma Human Papillomavirus Anal Infection." *Journal of Infection* 73, no. 4 (October): 380–83. https://doi.org/10.1016/j.jinf.2016.07.006.

Chapter Three

Methodology

3.1 Research Design

The research was a systematic review that includes an observational and experimental studies that involve women of reproductive age, living with HIV in Africa and HPV self-sampling. The study was conducted December 2021. The search range was from January 0,1, 2000 to December 01, 2021.

Keywords

Human papillomavirus, Self-sampling, women living with HIV/AIDS, Africa

3.2 Population of the Study

The study population comprised of studies on HPV self-sampling among women of the reproductive age living with HIV conducted in African countries.

3.2.1 Inclusion Criteria

Studies on HPV self-sampling among women of the reproductive age living with HIV in Africa,

3.2.2 Exclusion Criteria

Studies on clinician sampling, women whose HIV/AIDS status are not known.

3.3 Sample and Sampling Techniques

The study area focused on studies conducted in Africa. Africa is the second-largest continent with an estimated 1.37 billion people, or 14% of the world's population (in 2021). Africa contributed to far more than a quarter of all cervical cancer deaths, making cervical cancer the continent's biggest cause of death

in women.[131, 132] The prevalence rate of cervical cancer is highest in Africa [131]. Around 36.7 million people worldwide are infected with HIV, including 2.1 million children. Around 25.5 million of the infected live in sub-Saharan Africa. In 2016, there were 730,000 AIDS-related deaths in the region. More than two-thirds of new HIV infections worldwide are in sub-Saharan Africa. This is the region most affected by the HIV / AIDS pandemic. The reasons that contribute to an increased susceptibility to HIV in sub-Saharan Africa are as a result of poverty, labour migration, urbanisation, gender inequalities and gender–based violence.

Sampling Techniques

Search Terms used to get data are derived from the Medical Subject Headings (MeSH). MeSH is a controlled vocabulary of biomedical- and health-related terms to describe the subject of a journal article. The terms are standardized keywords, from the US National Library of Medicine. MeSH terms were developed from Pubmed on human papillomavirus, self-sampling, HIV, women, Africa and these were used for searches from different databases.

3.4 Description of the Research Instrument

The research instrument used for the review was the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. It is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses. The PRISMA statement consists of a 27-item checklist and a 4-phase flow diagram

3.5 Data Collection

Synthetic Tools and Technique used for all search records is EndNote. It was used to check for duplication. After removing duplicates, the remaining records were screened for abstract and title using a set of inclusion criteria developed using the PICOTS framework (Population, Intervention, Comparisons, Outcomes, Time, Studies)[134]. Firstly, abstract and title screening using the inclusion criteria was used, followed by a review of the remaining full-text publications using both the inclusion and exclusion criteria. Two review authors (F.T, OA,) independently assessed the eligibility and methodology quality of

all the potential studies we identified as a result of the search strategy. We resolved the disagreement through discussion

All of the full-text articles were filtered and sorted in ENDNOTE. Excluded articles were labelled with the reason for exclusion, while included articles were labelled by relevant categories according to the purpose and domain of the study. The relevant categories were acceptability of HPV self-sampling, HPV self-sampling among HIV women in Africa, and cervical cancer screening among women of reproductive age living with HIV. Following the completion of the full-text screening, articles with identical authors were reviewed to ensure that all studies presented unique data without duplication.

The final included articles and their category labels were exported to spreadsheets. All included articles had basic information extracted: First Author name, Publication Year, Title of Journal, Period of participants' recruitment, Region of recruitment, Site of study, City/Area, Sample Size, Study Design, Population type, Inclusion criteria, Exclusion criteria, Type of Analysis, Number of participants who took up cervical cancer screening service, Number of times participants took up the cervical cancer screening service, Number of persons that reported social harms/ adverse effects due to the cervical screening, Social harms / adverse effects reported, Number of HPV positive persons, Number of HPV positive persons that were treated for cervical lesions and the Number of HPV persons that had linkage to care. For each relevant category, relevant articles were reviewed with key findings documented.

3.6 Data Analysis

The full search summary is presented in the Transparent Reporting of Systematic Reviews and Meta-analyses (PRISMA) flow diagram shown in Figure 4.0. A total of 1074 records were identified through electronic searches. After the removal of duplicates, 1008 records remained for eligibility screening.

Following the abstract review, 1074 full-text articles were screened using the inclusion criteria.

Subsequently, in a full-text review, 1067 of the 1074 articles were screened out by applying the exclusion criteria. A summary of the number of full-text articles and their reasons for exclusion are presented in

Figure 1. 99.3% of the records were excluded because there was either no HPV self-sampling or the purpose of the study was not to study HPV screening.

3.7 Ethical Approval

In contrast to quantitative and qualitative research, systematic review does not involve getting participants extremely private, delicate, or confidential information. Evidence for the systematic review study was provided through public available materials. However, before the commencement of the research, institutional ethics permission was collected at Lead City University for the systematic evaluatio

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

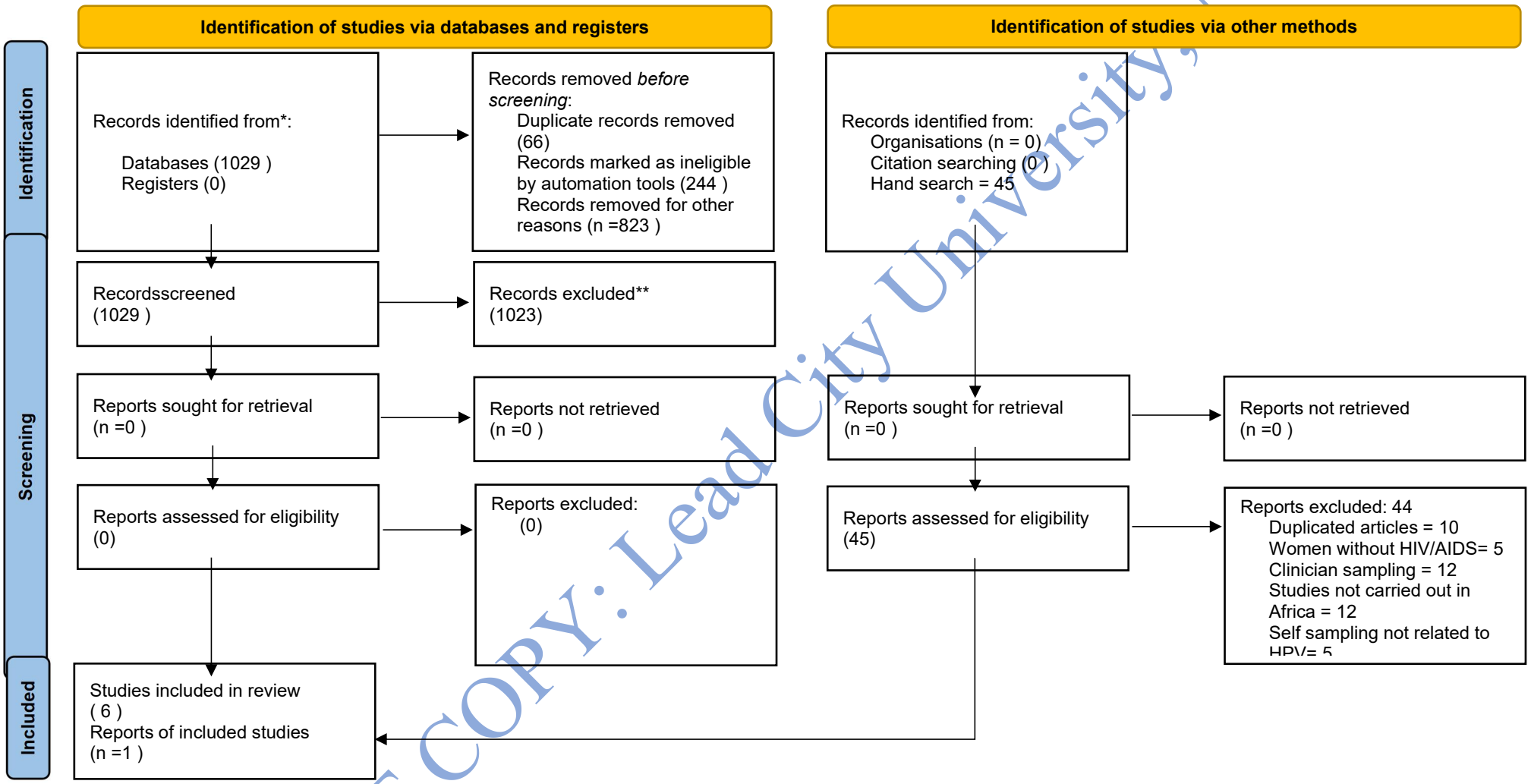


Figure 4.0

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. DOI: 10.1136/BMJ.n71. For more information, visit:http://www.prisma-statement.org/

Endnote

131. Frampton, G. K., Livoreil, B., & Petrokofsky, G. 2017. Eligibility screening in evidence synthesis of environmental management topics. Environmental Evidence, 6(1), 1-13.

S/N	FIRST AUTHOR'S NAME	YEAR	TITLE	STUDY DESIGN	COUNTRY
1.	Sheona M. Mitchell	2017	Self-collection based HPV testing for cervical cancer screening among women living with HIV in Uganda: a descriptive analysis of knowledge, intentions to screen and factors associated with HPV positivity	Cross-sectional survey	Uganda
1 2.	Tamara Elliott	2019	Performance of vaginal self-sampling for human papillomavirus testing among women living with HIV in Botswana	Cross-sectional pilot study	Botswana
3.	Philip E. Castle	2019	High-risk human papillomavirus prevalence in self-collected cervicovaginal specimens from human immunodeficiency virus (HIV)-negative women and women living with HIV	Cross-sectional	Botswana

Chapter Four

Results and Discussion of Findings

4.1 Demographic Data Analysis

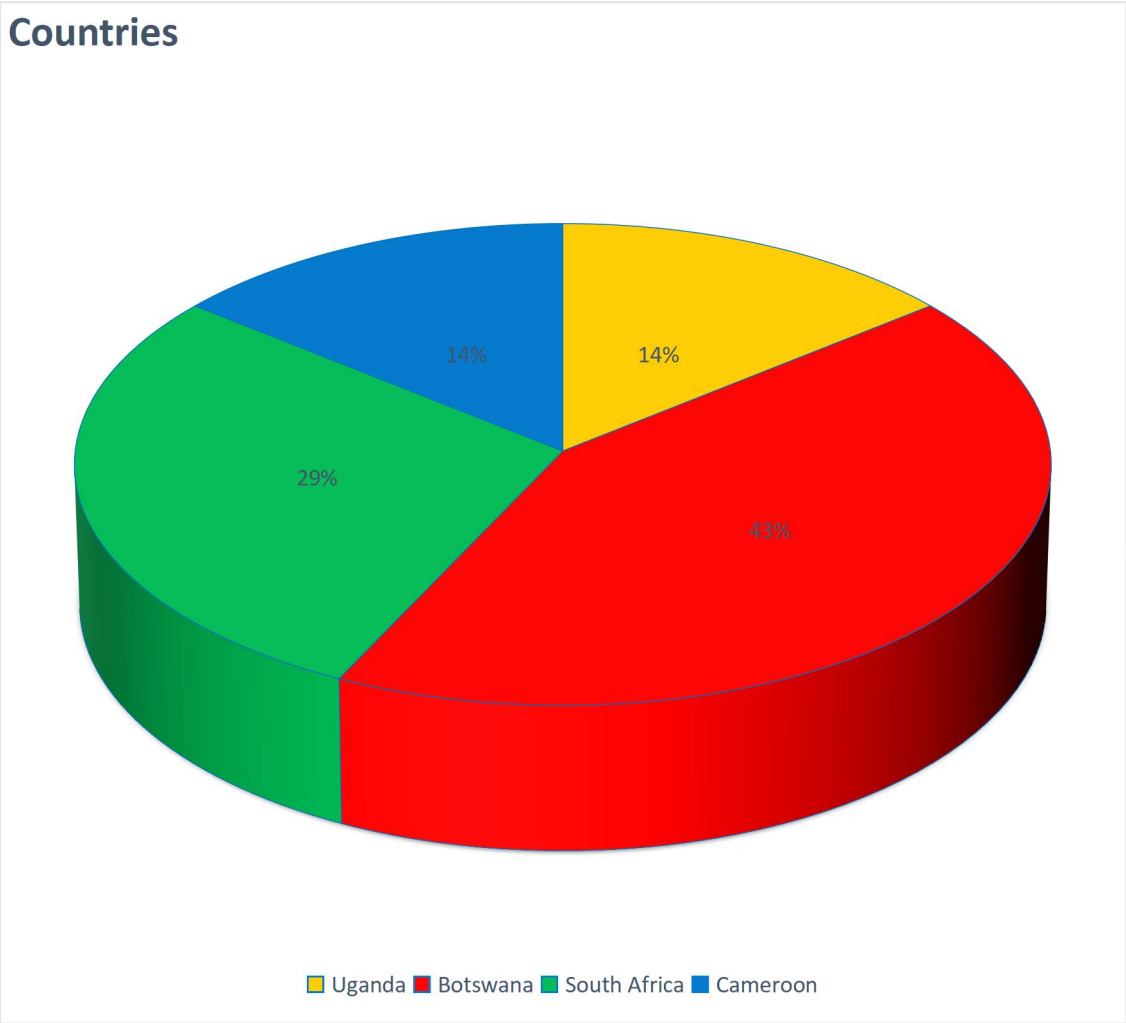
Description of Included Studies

After applying the screening criteria, 7 studies were eligible for inclusion in this review (Table 1.1) and were analysed. The acceptability and participation category had 5 publications, Comparison of HPV self-sampling versus clinician sampling testing category had 2 publications, uptake of cervical cancer screening services category had 5 publications, frequency of cervical cancer screening category had no publication, clinician assessment or treatment of cervical lesion or HPV positive category had 5 publications and social harm/ adverse effects of HPV self-sampling category had 2 publication.

Study designs were predominantly cross-sectional design (71.4%), but there is one cohort study (14.3%) and one exploratory descriptive qualitative (14.3%)

			living in Botswana		
4.	Kay Mahomed	2014	Human papillomavirus (HPV) testing on self-collected specimens: perceptions among HIV positive women attending rural and urban clinics in South Africa	Cohort	South Africa
5.	Paul C. Adamson	2015	Acceptability and Accuracy of Cervical Cancer Screening Using a Self-Collected Tampon for HPV Messenger-RNA Testing among HIV Infected Women in South Africa	Cross-sectional	South Africa
6.	Racquel E. Kohler	2018	HPV self-sampling acceptability and preferences among women living with HIV in Botswana	Cross-sectional	Botswana
7.	Amanda J. Pierz	2021	Acceptability of Self-Sampling for Cervical Cancer Screening Among Women Living With HIV and HIV-Negative Women in Limbé, Cameroon	Exploratory descriptive qualitative	Cameroon

(summary of studies Table 4.1)



4.2 Presentation of Data

Eligibility Criteria

PICOTS (Population, Intervention, Comparisons, Outcomes, Time, Studies) (Table 4.2)

Population	Women of reproductive age living with HIV in Africa
Intervention	Self-Sampling test for HPV
Comparisons	Clinician-sampling collection
Outcomes	Acceptability of HPV self-sampling and uptake of cervical cancer screening services
Time	1/1 /2000 to 1/12/2021

Participation Studies (Table 4.3)					
S/N	FIRST AUTHOR'S NAME	POPULATION	STUDY INTERVENTION	SCREENER	PARTICIPATION
1.	Sheona M. Mitchell	HIV positive women attending the Kisenyi Health Unit aged 30–69 years old,	Self-sampling at the HIV clinic	Self	40 participated out of 87 WHIV offered self-collection
2.	Tamara Elliott	HIV-positive women ≥25 years attending an HIV clinic	Self and clinician-sampling at the clinic	Self and clinician	All approached women participated
3.	Philip E. Castle	Women living with HIV and women that are HIV negative	Self-sampling at the HIV clinic	Self	Women were recruited in equal (20%) proportions, between 203–206 participants from five health facilities

Studies	Observational, Experimental, Cohort, Cross-Sectional

Studies took place in four countries, with Botswana and South Africa having the most with three and two, respectively. All studies consented to participants and had ethics approval from governing bodies. HPV testing was performed in five studies (71.4%), and the sampling methods varied by the study: self-sampling alone (42.9%), participants' opinions on self-sampling collected by questionnaire alone (28.6%), self-sampling and clinician-sampling collected (57.1%),

All the samples were collected at the clinic.

4.	Kay Mahomed	HIV positive patients attending two HIV treatment clinics	Self-sampling at the HIV clinic	Self	All women that were approached were willing to participate
5.	Paul C. Adamson	HIV-infected women seeking care at a government HIV clinic	Self and clinician-sampling at the clinic	Self and clinician	All approached women participated
6.	Racquel E. Kohler	WLWH aged 25 years or older attending an infectious disease clinic	Self and clinician-sampling at the clinic	Self and clinician	All approached women participated
7.	Amanda J. Pierz	WLWH and HIV[-] women attending the Outpatient Department (OPD)	Self and clinician at a private room at Limbe Regional Hospital	Self and clinician	585 WLWH and 292 HIV[-] women participated

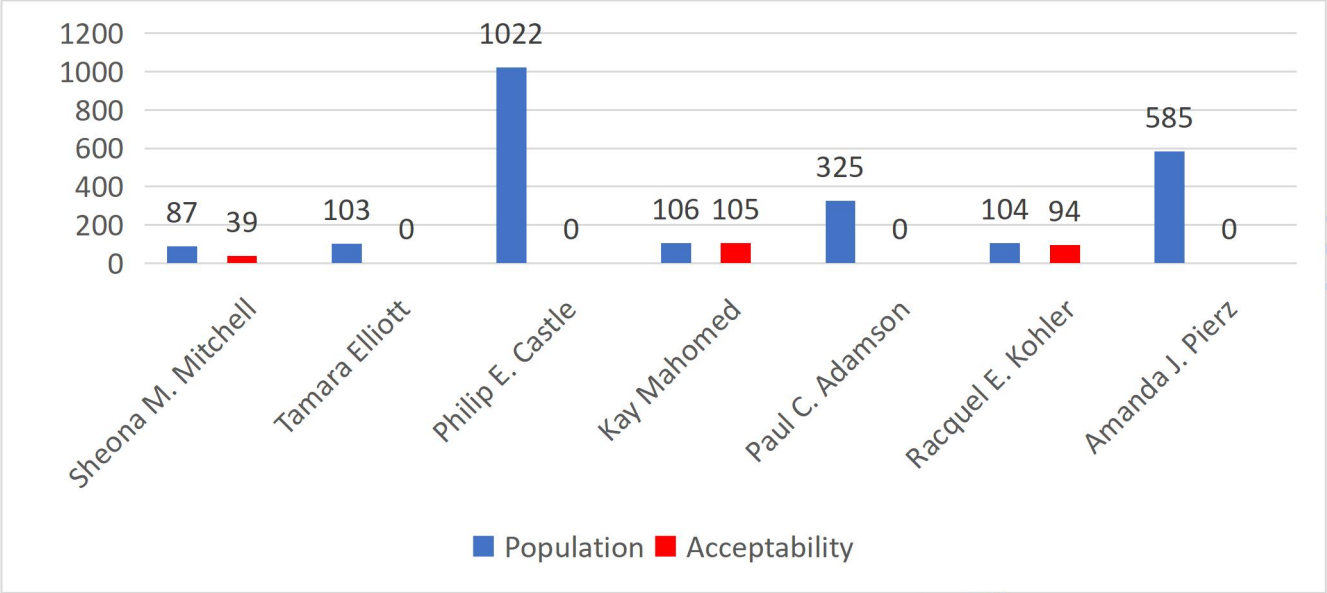
4.2.1 Research Questions

Acceptability of HPV Self-Testing

Five studies reported outcomes on acceptance of HPV self-sampling Sheona M. Mitchell et al, Kay Mahomed et al, Paul C. Adamson et al, Racquel E. Kohler et al and Amanda J. Pierz et al. From the articles that reported outcomes on the acceptability of HPV self-sampling most of the women found self-collection for cervical cancer screening to be acceptable Sheona M. Mitchell et al.,(97.5%, 39/40), Kay Mahomed et al, (94.0 %, 99/105) Paul C. Adamson et al, (77% 255/25), and Racquel E. Kohler (95.2%, 99/104). Kay Mahomed et al reported that HPV testing may be an acceptable way to improve coverage for cervical cancer screening in high-risk HIV-seropositive women, also the findings presented by Amanda J. Pierz et al study demonstrated the acceptability of self-collection. In the study by Racquel E. Kohler et al, (95.2%) 99 of the women said they would test again via self-sampling.

	FIRST AUTHOR'S NAME	POPULATION	TESTING PERFORMED	COLLECTION PREFERENCE/ ACCEPTABILITY	CONCLUSION
	Sheona M. Mitchell	HIV positive women attending the Kisenyi Health Unit aged 30–69 years old,	HPV self-testing	Participants (n=40): self-HPV (n=39).	Almost all WHIV found self-collection for cervical cancer screening to be acceptable
	Tamara Elliott	HIV-positive women ≥25 years attending an HIV clinic	hr-HPV	None	None
	Philip E. Castle	Women living with HIV and women that are HIV negative	Self HPV	None (n=1022): WLHIV(570)	None
	Kay Mahomed	HIV positive patients attending two HIV treatment clinics	Self HPV	Participants (n=105) Self-HPV (n=99; 94%) preferred self –sampling	Patient self-collection with HPV Testing may be an acceptable way to improve coverage of cervical cancer screening in high-risk HIV-seropositive women.
	Paul C. Adamson	HIV-infected women seeking care at a government HIV clinic	Self and clinician-HPV	Participants (n=325) Self-HPV (n=255; 75%) Clinician-HPV (n= 49, 15.1%))	Self-collection is acceptable to women and has similar hrHPV mRNA positivity rates as clinician-collection
	Racquel E. Kohler	WLWH aged 25 years or older attending an infectious disease clinic	Self-HPV	Participants (n=104) Self-HPV(n= 99, 95.2%)	HPV self-sampling is acceptable among WLWH
	Amanda J. Pierz	WLWH and HIV[-] women attending the Outpatient Department (OPD)	None	All participants indicated that self-sampling was an acceptable method of specimen collection.	The findings presented in this paper demonstrate the acceptability of self-collection for specimens within our study community in Limbé, Cameroon.

Summary of Acceptability Studies (Table 4.4)



Acceptability of HPV self-sampling

Comparison of Self-Sampling and Clinician Sampling

Two of the studies included in the review compared the two sampled tests. Tamara Elliott et al showed a high agreement of 95% between self and clinician sampled tests while Paul C. Adamson showed a moderate agreement of 77.6% between the two sampled tests.

S/N	FIRST AUTHOR'S NAME	COUNTRY	TYPES OF HPV DETECTED	HPV PREVALENCE (%)		AGREEMENT BETWEEN SS AND CS (%)
				SS	CS	
1	Sheona M. Mitchell	Uganda	Hr-HPV and HPV 16 ,18	18 (45.0%)	Nil	Nil
2.	Tamara Elliott	Botswana	Hr-HPV	28	24	95%
3.	Philip E. Castle	Botswana	Hr-HPV	570	-	-
4.	Kay Mahomed	South Africa	-	99	7	-
5.	Paul C. Adamson	South Africa	hrHPV and mRNA	138	116	77.6%
6.	Racquel E. Kohler	Botswana	Hr-HPV	32	-	-
7.	Amanda J. Pierz	Cameroon	-	-	-	-

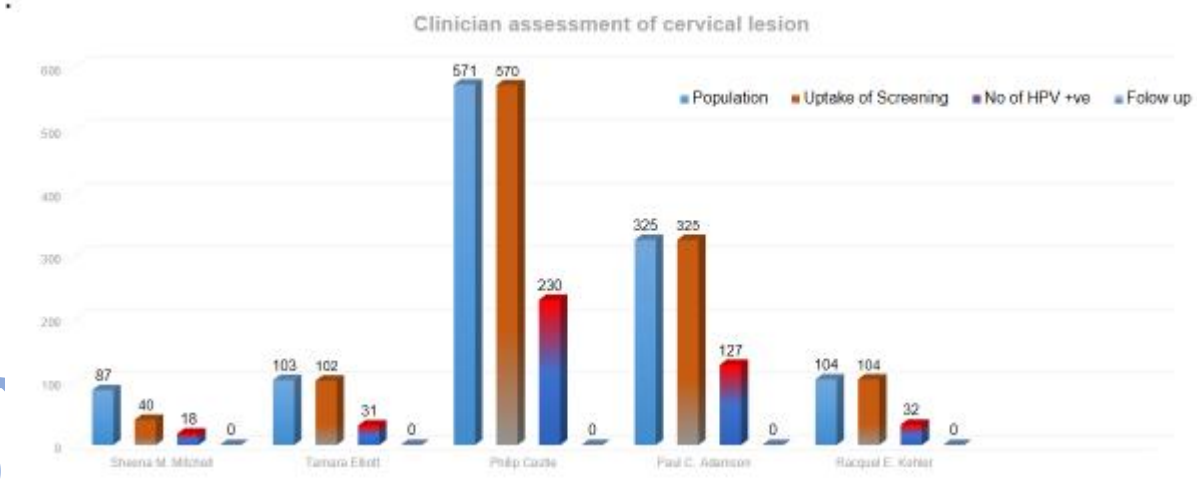
Comparison of HPV self-sampling versus clinician sampling testing (Table 4.5)

Uptake of Self-Sampled HPV Screening

Five of the studies included in the review reported uptake of self-sampling as the proportion of those offered HPV testing who accepted and completed screening in each study. In all the reviewed studies after subjects consented and were randomized, they were told to get their self-sampling at the designated place in the clinic. In Paul C. Adamson et al and Racquel E. Kohler et al, all participants took part in the screening (325/325 and 104/104) respectively. Whereas, in Tamara Elliott et al and Philip E. Castle et al only one person did not take part in the screening. However, this was different in Sheona M. Mitchell et al., where only 47.6% (40/84) women of took the screening

S/N	FIRST AUTHOR'S NAME	PARTICIPANTS (n)	UPTAKE OF CC SCREENING (n)	UPTAKE OF CC SCREENING (%)	NUMBER OF +VE HPV
1.	Sheona M. Mitchell	84	40	98.8%	18 (45.0%)
2.	Tamara Elliott	103	102	99.0%	31 (30.0%)
3.	Philip E. Castle	1022 (571 WLWH and 451 HIV-negative women)	570	99.8%	230
4.	Kay Mahomed	106	-	-	-
5.	Paul C. Adamson	325	325		127
6.	Racquel E. Kohler	104	104		32
7.	Amanda J. Pierz	585	-	-	-

Uptake of Cervical Cancer Screening Services (Table 4.6)



Clinician Assessment or Treatment of Cervical Lesion or HPV Positive

Five studies reported the proportion of those women who got a positive result (Sheona M. Mitchell 18, Tamara Elliott 31, Philip E. Castle 230, Paul C. Adamson 127, Racquel E. Kohler 32) and reached a health centre for further treatment or recommendation.

S/N	FIRST AUTHOR'S NAME	PARTICIPANTS (n)	PARTICIPANTS TESTED +VE (n)		LINKAGE TO CARE (n)	CARE RECOMMENDED	FOLLOW UP
1.	Sheona M. Mitchell	87	18	5	colposcopy assessment		-
2.	Tamara Elliott	103	31	10 (30.00 %)	Colposcopy		-
3.	Philip E. Castle	1022 (571 WLWH and 451 HIV-negative women)	230		Those with suspected cancer were referred to colposcopy and biopsy and based on those results were then referred for care.		-
4.	Kay Mahomed	106	-	-	-		-
5.	Paul C. Adamson	325	127	-	Women were referred for Colposcopy		-
6.	Racquel E. Kohler	106	32	-	Participants testing positive for any hr-HPV (from self- or provider-sample) were counselled over the phone and scheduled for follow-up colposcopy.		-
7.	Amanda J. Pierz	585	-	-	-		-

Clinician Assessment or Treatment of Cervical Lesion or HPV Positive (Table 4.7)

Social Harm/ Adverse Effects

Out of the 7 reviewed articles only two studies reported the proportion of those women who had physical discomfort, pain or feel embarrassed during the sampling collection. In Paul C. Adamson et al study 7% had physical discomfort, 3% were embarrassed with the self-sampling test while 36% had physical discomfort and 3% were embarrassed with the clinician-sampling test.

Whereas Racquel E. Kohler et al reported that the mean value of women who reported having physical discomfort was 1.35, pain 1.9 and embarrassment was 1.32 from self-sampling while from clinician-sampling physical discomfort was 1.32, pain 1.17 and embarrassment was 1.13.

Frequency of Cervical Cancer Screening

No study reported comparative data on the frequency of cervical cancer screening.

4.3 Discussion of Findings

In Sheona M. Mitchell et al study, 39 out of 40 participants accepted HPV self-sampling. In kay Mahomed et al study he concluded that patient self-collection with HPV testing may be an acceptable way to improve coverage of cervical cancer screening in high-risk HIV-seropositive women as most of the participants agreed to be self-sampled.

Furthermore, Racquel E. Kohler and Amanda J. Pierz reported the acceptable of HPV self-sampling among Women living with HIV in their studies.

Overall, self-sampling for HPV testing seems acceptable to the majority of women and produces reasonably high screening participation rates. The women found the self-sampling device easy to use, said they would prefer self-sampling in the future to clinician-sampling screening and that they would love to test again in the future. Another review also shows that HPV self-sampling is highly accepted as the participants found it easy and convenient [137]

Self-sampling of HPV has the potential to increase access to screening, overcome some of the psychosocial barriers that limit testing, and increase screening uptake.

Table 7 shows the number of participants that tested positive for high-risk HPV during the studies by Sheona M. Mitchell et al (18), Tamara Elliott (31), Philip E. Castle(230), and Paul C. Adamson(127), Racquel E. Kohler(32). From the five studies that reported tested positive participants only two reported follow up. Sheona M. Mitchell et al reported 5 out of 10 tested positives received care while Tamara Elliott et al reported 10 participants were linked to care out of the 31 that were tested positive. Those with suspected cancer were referred to colposcopy and biopsy.

The follow up was not encouraging. Furthermore, the overall low rate of medical treatment after positive screening results is of concern.

All the included studies did not report the frequency of screening.

However, given that cervical screening is recommended at most every 5 years, it is understandable that studies generally did not assess this longer-term outcome. This review adds on evidence from a systematic review in Africa showing concordance of HPV-self sampling and physician collected samples[136].

In addition, two studies reported social harm/adverse effects of self- clinician sampled test. Paul C. Adamson et al and Racquel E. Kohler et al reported slight physical discomfort, pain and embarrassment during the sampling collection (Table 8).

The result of this review shows that the social harm/adverse effect was minimal as few people complained of feeling embarrassed, discomfort or in pain for the two collection methods.

Two studies included in the review show a high agreement between self and clinician sampled tests.

Finally, the participants in the review studies were HIV-infected women seeking care at the government HIV clinic, infectious disease clinic, Outpatient Department (OPD), Health Unit

or HIV clinic therefore, the uptake of cervical screening service should be feasible. The review of the studies shows higher uptake of cervical cancer screening. In Paul C. Adamson et al and Racquel E. Kohler et al all their participants took up the screening, this shows that the uptake of cervical cancer screening is high in their studies and Tamara Elliott et al (102/103) only one person couldn't take the screening because she was pregnant at the time of the study.

In contrast, 40 participants out of 87 took up the screening in Sheona M. Mitchell et al study. This is because few could not be reached by phone, some indicated that they had screened for cervical cancer elsewhere, and others refused to attend the clinic due to the far distance to travel. The results of this review are in agreement with a previous systematic review showing higher uptake of cervical cancer screening service[138].

Endnotes

[131] Mitchell, S. M., Pedersen, H. N., Stime, E. E., Sekikubo, M., Moses, E., Mwesigwa, D., ... & Ogilvie, G. S. 2017. Self-collection based HPV testing for cervical cancer screening among women living with HIV in Uganda: a descriptive analysis of knowledge, intentions to screen and factors associated with HPV positivity. *BMC women's health*, *17*(1), 1-10.

[132] Elliott, T., Kohler, R. E., Monare, B., Moshashane, N., Ramontshonyana, K., Muthoga, C., ... & Ramogola-Masire, D. 2019. Performance of vaginal self-sampling for human papillomavirus testing among women living with HIV in Botswana. *International Journal of STD & AIDS*, *30*(12), 1169-1176.

[133] Castle, P. E., Varallo, J. E., Bertram, M. M., Ratshaa, B., Kitheka, M., & Rammipi, K. 2020. High-risk human papillomavirus prevalence in self-collected cervicovaginal specimens from human immunodeficiency virus (HIV)-negative women and women living with HIV living in Botswana. *PloS one*, *15*(2), e0229086.

[134] Mahomed, K., Evans, D., Sauls, C., Richter, K., Smith, J., & Firnhaber, C. 2014. Human papillomavirus (HPV) testing on self-collected specimens: perceptions among HIV positive women attending rural and urban clinics in South Africa. *The Pan African medical journal*, *17*.

[135] Adamson, P. C., Huchko, M. J., Moss, A. M., Kinkel, H. F., & Medina-Marino, A. 2015. Acceptability and accuracy of cervical cancer screening using a self-collected tampon for HPV messenger-RNA testing among HIV-infected women in South Africa. *PloS one*, *10*(9), e0137299.

[136] Kohler, R. E., Elliott, T., Monare, B., Moshashane, N., Ramontshonyana, K., Chatterjee, P., ... & Morroni, C. 2019. HPV self-sampling acceptability and preferences among women living with HIV in Botswana. *International Journal of Gynecology & Obstetrics*, *147*(3), 332-338.\

[137] Pierz, A. J., Ajeh, R., Fuhngwa, N., Nasah, J., Dzudie, A., Nkeng, R., & Adedimeji, A. 2021. Acceptability of Self-Sampling for Cervical Cancer Screening Among Women Living With HIV and HIV-Negative Women in Limbé, Cameroon. *Frontiers in Reproductive Health*, *2*, 13.

Chapter Five

Conclusion

5.1 Summary of Findings

Screening methods such as cytology and clinician-collected HPV testing that are available and accepted to detect women at risk for pre-cancer are not accessible to the majority of women living with HIV in Africa. Given the slow progression from HPV infection to pre-cancerous lesions and invasive cancer, there is a call for intervention.

Alternative screening strategies that decrease structural and other access challenges faced by women include self-sampling for HPV, as it is a simple intervention that women can use which supports their right to health. It also grants privacy and convenience to women, bypassing common barriers.

HPV self-sampling is found to be more acceptable as it overcomes personal barriers such as embarrassment, and reluctance in letting a clinician see or touch their genitals [134].

Of the seven included articles, five articles reported the acceptability of self-sampled tests compared to clinician-sampled tests. Most women living with HIV in Africa preferred to have their samples collected themselves, there is no significant difference in the results of the two-collection method. More so, the self-sampling test can be done at their convenient time and the result of the test can be communicated to them through mail or phone call. This will make it easier for them to assess cervical cancer screening.

5.2 Conclusion

This systematic review found that no treatment for cervical cancer lesions and HPV positive were given to HIV-positive women who were tested positive. HPV self-sampling is an effective and achievable substitute for clinician-sampling in Africa. HPV self-sampling eradicates the barrier of being embarrassed therefore it was preferred to clinician sampling. It could improve the uptake of cervical cancer screening and reduce the mortality rate of cervical cancer in Africa.

5.3 Recommendation

HPV self-sampling should be integrated into routine HIV care at a community level. Cervical cancer is preventable cancer to prevent HPV from developing into cervical cancer, clinical assessment or treatment should be provided to participants who tested HPV positive during the studies.

5.4 Contribution to Knowledge

The research has shown that to reduce prevalence of cervical cancer, HPVself-sampling which was the most acceptable screening needs to be encouraged among HIV positive women. Furthermore, the study has contributed to knowledge by showing the need for researcher to provide treatment for their patients who were tested and provide important information on the HPV self-testing.

5.5 Suggested Area of Further Research

This review suggested that further studies on the systematic review of qualitative studies exploring participants' experiences of self-sampling and impact on discrimination or other social harms should be done. Also, on the frequency of cervical cancer screening and barriers to self-sampling of HPV