Cancer prevention
in women living with HIV in sub-Saharan Africa

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Cancer prevention in women living with HIV in sub-Saharan Africa

PhD Thesis submitted by

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- Pages 145–150 (printed pages 140–145) have been redacted to protect personal information (Curriculum Vitae).
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ACKNOWLEDGMENTS

"If you want to go fast, go alone. If you want to go far, go together." African proverb

This has been a dynamic journey. I always like to refer to it as a roller-coaster: with so many ups and downs, followed by fear but also excitement and adrenaline. To be honest, I faced some really difficult moments, especially in the last six months of this journey. Reflecting back now, I realize that you learn the most about the life, humanity and yourself, during your most difficult periods. This journey has profoundly changed me, strengthened my relationship with family and friends, but also brought many amazing souls into my life. **Here, I want to cherish you all.** Your impact on my life has been and continues to be tremendous. I will always be thankful for sharing this journey with you.

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go to **Dr. Mazvita Sengayi-Muchengeti**, who was there for me from the very first day. Your kindness and patience greatly enriched my journey. I have always admired the ease with which you manage to be such a fantastic researcher and an inspiring leader. Your hospitality in South Africa was one of my favorite experiences during this journey and, I will always be grateful for the opportunity to visit the National Cancer Registry. I would like to express my gratitude to **Dr. Per von Groote** for introducing me to the world of implementation science. You were always there to provide fresh perspective and critical feedback, genuinely caring about my PhD progress. I would also like to extend my sincere thanks to **Prof. Dr. Annika Frahsa** for her role as a GHS representative and external examiner, and for chairing my thesis defense. Thank to entire **GHS** team as well for their invaluable assistance and guidance in this final step.

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The last five years were the best years of my life. I appreciate the support, encouragement, kindness, and love you all have offered me over the last five years. Thank you for sharing this journey with me. I look forward to the great moments and opportunities that await me, both professionally and personally.

Thank you!

Danke schön!

Hvala vam!

Maša, July 2024

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SUMMARY

Background

Sub-Saharan Africa is the epicenter of the HIV epidemic, where women are disproportionately affected compared to men. With widespread antiretroviral therapy (ART), life expectancy for those living with HIV is improved, allowing them to reach ages at which cancers may develop. Cervical and breast cancers are the main causes of cancer-related morbidity and mortality among women in the region. To address these major health challenges, the World Health Organization (WHO) has launched two global initiatives: the Cervical Cancer Elimination Initiative and the Global Breast Cancer Initiative (GBCI). In 2020, WHO released the global strategy to eliminate cervical cancer within the century, setting three targets for each country to achieve by 2030: 90% of girls fully vaccinated against HPV by age 15; 70% of women screened by age 35 and again by age 45; and 90% of women with cervical disease receiving appropriate treatment. Established in 2021, the GBCI aims to reduce breast cancer mortality by 2.5% per year in low- and middle-income countries, proposing strategies to improve health promotion and early detection, timely diagnosis, and breast cancer management. Women living with HIV face significant disparities in cervical and breast cancer care and outcomes. They are six times more likely to develop cervical cancer and often at a younger age than the general population, mainly due to persistent high-risk HPV infections, difficulties in clearing these infections, and a faster progression to cervical pre-cancer and cancer. Additionally, they have higher rates of treatment failure and recurrence of cervical pre-cancer compared to women without HIV. This disease burden is especially relevant in sub-Saharan Africa, where the majority of women living with HIV and cervical cancer reside. Women living with HIV, while not at higher risk for breast cancer, have lower survival rates than those without HIV. Additionally, women in sub-Saharan Africa generally have lower breast cancer survival rates than those in high-income countries. In this thesis, I delve into the disparities in breast and cervical cancer in women living with HIV in sub-Saharan Africa. I present the cancer prevention and care continuum as a framework to describe interventions for primary, secondary and tertiary prevention. I also explore various aspects of this continuum, with a particular focus on cervical and breast cancer in women living with HIV in sub-Saharan Africa.

Aims

The overall aim of my thesis was to study the two most common cancers in women in sub-Saharan Africa: cervical and breast cancer in women living with HIV. Specifically, this thesis aimed to describe current national cervical cancer control policies (**Publication 2**), to evaluate practices and outcomes of cervical cancer prevention and care programs (**Publication 3**), and to develop a tool for improving data collection for these programs (**Publication 1**) offered on- or off-site at ART clinics in this region. Also, it aimed to understand and investigate epidemiology of breast cancer among women living with and without HIV in South Africa (**Publication 4**).

Methods

This thesis embodies quantitative and mixed-methods studies to explore different aspects of the cervical and breast cancer prevention and care continuum for women living with HIV in sub-Saharan Africa. In **Publication 1**, I used a Delphi methodology to achieve consensus among stakeholders on indicators and the minimum data set required to assess the performance of cervical cancer prevention and care services at HIV clinics across sub-Saharan Africa. The consensus process, conducted from February 2021 to March 2022, consisted of three iterative online rounds involving questionnaires, followed by a virtual stakeholders' meeting with four satellite sessions. Experts were invited to adapt the indicators to their context (round 1), rate them based on five criteria using a 5-point Likert-type scale (rounds 2 and 3), and then rank the indicators by importance (round 3). In **Publication 2**, my contribution involved reviewing cancer control policies in African countries with an HIV prevalence of 10% or more in 2018. Our search included Medline via PubMed, the International Cancer Control Partnership website, and the national governmental websites. This search was supplemented with expert consultations from each of the included countries, as in these settings policy documents are not always publicly available. We then synthesized the aspects outlined in the policies across different steps of the cervical cancer prevention and care continuum and reported on recommendations, specifically those tailored to p living with HIV. In **Publication 3**, I contributed to a two-level facility-based survey in HIV clinics participating in the International epidemiology Databases to Evaluate AIDS (IeDEA) consortium in sub-Saharan Africa, conducted between November 2020 and July 2021. The survey included at site-level assessment of

cervical cancer prevention and care services, and a patient-level analysis of data from routine care. The survey was developed together with local and WHO experts, and based on insights received through face-to-face meetings with stakeholders and during the field visit. In **Publication 4,** I analyzed the characteristics of breast cancer cases in women aged 15 years and older, both living with and without HIV, diagnosed with cancer in the South African public healthcare sector from 2004 to 2014. Cancer records were obtained from the South African National Cancer Registry, and HIV-related laboratory records from the National Health Laboratory Services Corporate Data Warehouse. I assessed the odds of being HIV positive versus HIV negative in relation to patient-, cancer-, and municipality-related characteristics.

Results

In the Delphi process presented in **Publication 1**, 105 experts from 15 sub-Saharan African countries or international organizations were invited to participate. Response rates were 34% in round 1, 40% in round 2, and 44% in round 3. I reviewed 39 policies from 21 African countries and seven from international organizations to extract and summarize available indicators. Experts reached consensus on 17 indicators in the following domains: primary prevention (HPV prevention, n=2), secondary prevention (screening, triage, treatment of cervical pre-cancer lesions, n=11), tertiary prevention (cervical cancer diagnosis and care, n=2), and long-term impact of the program and linkage to HIV service (n=2). These indicators measure the performance of cervical cancer prevention and care services and are tailored to programs offered on- or off-site at ART clinics. **Publication 2** presents results from the review of 33 policy documents from nine African countries with high HIV burden. This review found that all included countries had policies on cervical cancer prevention and control either as a standalone policy (78%), or as part of a cancer or non-communicable diseases policy (22%), or both (67%). Aspects of HPV vaccination were reported in seven of nine countries. For most aspects of primary prevention (sex education, condom use, warnings against tobacco use, school-based HPV vaccination strategy) were greatly homogenous in all investigated countries, but recommendations on voluntary male circumcision and HPV vaccination dose schedules for girls living with HIV were rarely reported. The most common recommended screening methods were visual inspection with acetic acid (VIA) (89%) and Pap smear (78%), and treatment methods included

cryotherapy (100%) and loop electrosurgical procedure (LEEP) (89%). Age at screening commencement and screening intervals for women living with HIV varied across countries, but other specific recommendations for cervical cancer prevention and care in women living with HIV were often lacking in investigated policies. Service costs for women and indicators disaggregated by HIV status for monitoring performance of cervical cancer programs were rarely reported. The facility-based survey presented in **Publication 3** was conducted in 30 sites across 14 countries in sub-Saharan Africa, achieving a 100% respond rate. The survey discovered that HPV vaccination was ongoing in only a third of the sites (33%). Screening services were routinely available in two thirds of the surveyed HIV clinics (67%), primarily using visual inspection with acetic acid (83%). Less than a quarter of sites consistently referred women for cervical screening (23%). Invasive cervical cancer diagnosis (69%) and treatment (67%) services were available in approximately two-thirds of the sites, often incurring costs (partially or in full) to the patients in more than half of them. Government funding for cervical cancer prevention received less than half of the sites (43%). Among the sites receiving non-governmental financial support, 43% was dedicated to support cervical cancer prevention (43%). Almost all sites used electronic systems to collect data (90%), though only half routinely collected cervical cancer data, including data needed to inform WHO indicators to monitor global targets for cervical cancer elimination in women living with HIV. In sites with available patient data, a significant gap was observed between the WHO target of 70% screening and 90% treatment for cervical pre-cancer and actual screening and treatment rates. In nation-wide South African study presented in **Publication 4** I evaluated 40 520 breast cancer cases in women aged 15 years and older diagnosed with breast cancer in a public health sector laboratory between 2004 and 2014 in South Africa. Of these, 73% had unknown HIV status, 19% were HIV negative, and 8% were HIV positive. The median age at breast cancer diagnosis was 43 years (interquartile range [IQR]: 37-52) in HIV positive and 57 years (IQR: 46-68) in HIV negative women, respectively. The odds of being HIV positive was higher in women who were aged 30-34 years compared to women aged 35-39 years at cancer diagnosis (odds ratio [OR] 1.38, 95% confidence interval [CI] 1.10-1.71), Black versus non-Black (OR 6.41, 95% CI 5.68-7.23), diagnosed with cancer in rural versus urban areas (OR 1.59, 95% CI 1.40-1.82) and diagnosed in municipalities with low and middle (OR 3.46, 95% CI 2.48-4.82) versus high socioeconomic position (OR 2.69, 95% CI 2.11-3.42).

Conclusion

In addressing the intersecting challenges of HIV, cervical cancer, and breast cancer, this thesis has markedly contributed to bridging critical knowledge gaps in cervical and breast cancer prevention and care continuum for women living with HIV in sub-Saharan Africa. This thesis, formed of four publications, provides a foundation for evidence-based interventions, emphasized by the development of facility-based indicators for monitoring, a critical review of national policy landscapes, and insightful analyses from comprehensive facility-based survey on cervical cancer prevention and care services, and a nation-wide study of breast cancer cases. These efforts have highlighted the urgent need for holistic and integrated approaches in tackling the dual burden of HIV and cancer, emphasizing the importance of accessible and sustainable health interventions for cervical cancer elimination and effective breast cancer control. Moreover, it calls for a global commitment to mobilize political support, improve healthcare systems, and engage communities in working together to achieve the goals of the WHO Cervical Cancer Elimination and Global Breast Cancer Initiatives in sub-Saharan Africa. This thesis not only enriches our understanding and knowledge of cancer prevention in women living with HIV in this region, but also paves the way for future research and actions to improve health outcomes for this vulnerable population.

ABBREVIATIONS

ACCHIVe	Advancing Cervical Cancer Screening in HIV-positive women
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
BC	Breast Cancer
BMI	Body Mass Index
CanScreen5	Cancer Screening in Five continents
CC	Cervical Cancer
CCPC Cascade	Cervical Cancer Prevention and Care Cascade
CDW	Corporate Data Warehouse
CIs	Confidence Intervals
CKC	Cold Knife Conization
COVID-19	Coronavirus Disease-19
DNA	Deoxyribonucleic acid
EP	Expert Panel
FBO	Faith Based Organization
GBCI	Global Breast Cancer Initiative
HDI	Human Development Index
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
IARC	International Agency for Research on Cancer
ICD-O-3	International Classification of Diseases for Oncology
IDCCP	Improving Data for Decision-making in Global Cervical Cancer Programs
IeDEA	International epidemiology Databases to Evaluate AIDS
IeDEA DES	IeDEA Data Exchange Standard
IQR	Interquartile range
LLETZ	Loop Excision of the Transformation Zone
LMICs	Low- and middle-income countries

NADCs	Non-AIDS-defining cancers
NCI	National Cancer Institute
NCR	National Cancer Registry
NGO	Non-Governmental Organization
NHLS	National Health Laboratory Services
ORs	Odds Ratios
PBCR	Population Based Cancer Registry
PEPFAR	United States President's Emergency Plan for AIDS Relief
PIs	Principal Investigators
REDCap	Research Electronic Data Capture
SAIMD	South African Multiple Deprivation Index
SEP	Socio-Economic Position
VIA	Visual Inspection with Acetic Acid
VIAC	Visual Inspection with Acetic Acid and Cervicography
VILI	Visual Inspection with Lugol's Iodine
WHO	World Health Organization
WLHIV	Women living with HIV

Gender language disclaimer

This publication uses the word "woman" (and the pronouns "she" and "her") to describe individuals whose sex assigned at birth was female, whatever their gender identity.

TABLES AND FIGURES

Figures in the Overall Background and Introduction, Methods, and Discussion

Tables in the Overall Background and Introduction

PREFACE

The presented thesis is a publication-based dissertation of four published papers, in line with the regulations of the Graduate School of Health Sciences, the Faculty of Medicine, and the Faculty of Human Sciences at the University of Bern, Bern, Switzerland.

1. **Davidović M**, Asangbeh SL, Taghavi K, Dhokotera T, Jaquet A, Musick B, Van Schalkwyk C, Schwappach D, Rohner E, Murenzi G, Wools-Kaloustian K, Anastos K, Omenge OE, Boni SP, Duda SN, von Groote P, Bohlius J; International Epidemiology Databases to Evaluate AIDS. Facility-based indicators to manage and scale up cervical cancer prevention and care services for women living with HIV in sub-Saharan Africa: a three-round online Delphi consensus method. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2024 Feb 1;95(2):170-8. https://doi.org/10.1097/QAI.0000000000003343
2. Asangbeh-Kerman SL, **Davidović M**, Taghavi K, Kachingwe J, Rammipi KM, Muzingwani L, Pascoe M, Jousse M, Mulongo M, Mwanahamuntu M, Tapela N, Akintade O, Basu P, Dlamini X, Bohlius J. Cervical cancer prevention in countries with the highest HIV prevalence: a review of policies. BMC public health. 2022 Aug 10;22(1):1530. https://doi.org/10.1186/s12889-022-13827-0
3. Asangbeh-Kerman SL, **Davidović M**, Taghavi K, Dhokotera T, Manasyan A, Sharma A, Jaquet A, Musick B, Twizere C, Chimbetete C, Murenzi G, Tweya H, Muhairwe J, Wools-Kaloustian K, Technau KG, Anastos K, Yotebieng M, Jousse M, Ezechi O, Orang'o O, Bosomprah S, Boni SP, Basu P, Bohlius J; International Epidemiology Databases to Evaluate AIDS. Cervical cancer prevention and care in HIV clinics across sub-Saharan Africa: results of a facility-based survey. Journal of the International AIDS Society. 2024 Jul;27(7):e26303. https://doi.org/10.1002/jia2.26303
4. **Davidović M**, Tafadzwa D, dos Santos Silva I, Bohlius J, Sengayi-Muchengeti M. Breast cancer in women by HIV status: A report from the South African National Cancer Registry. PLoS One. 2024 Jun 17;19(6):e0305274. https://doi.org/10.1371/journal.pone.0305274

Additionally, I include in supplementary chapters two peer-reviewed and two non-peer reviewed published publications relevant to my thesis. These additional works provide valuable insights into my research efforts and topics.

Peer reviewed and published publications

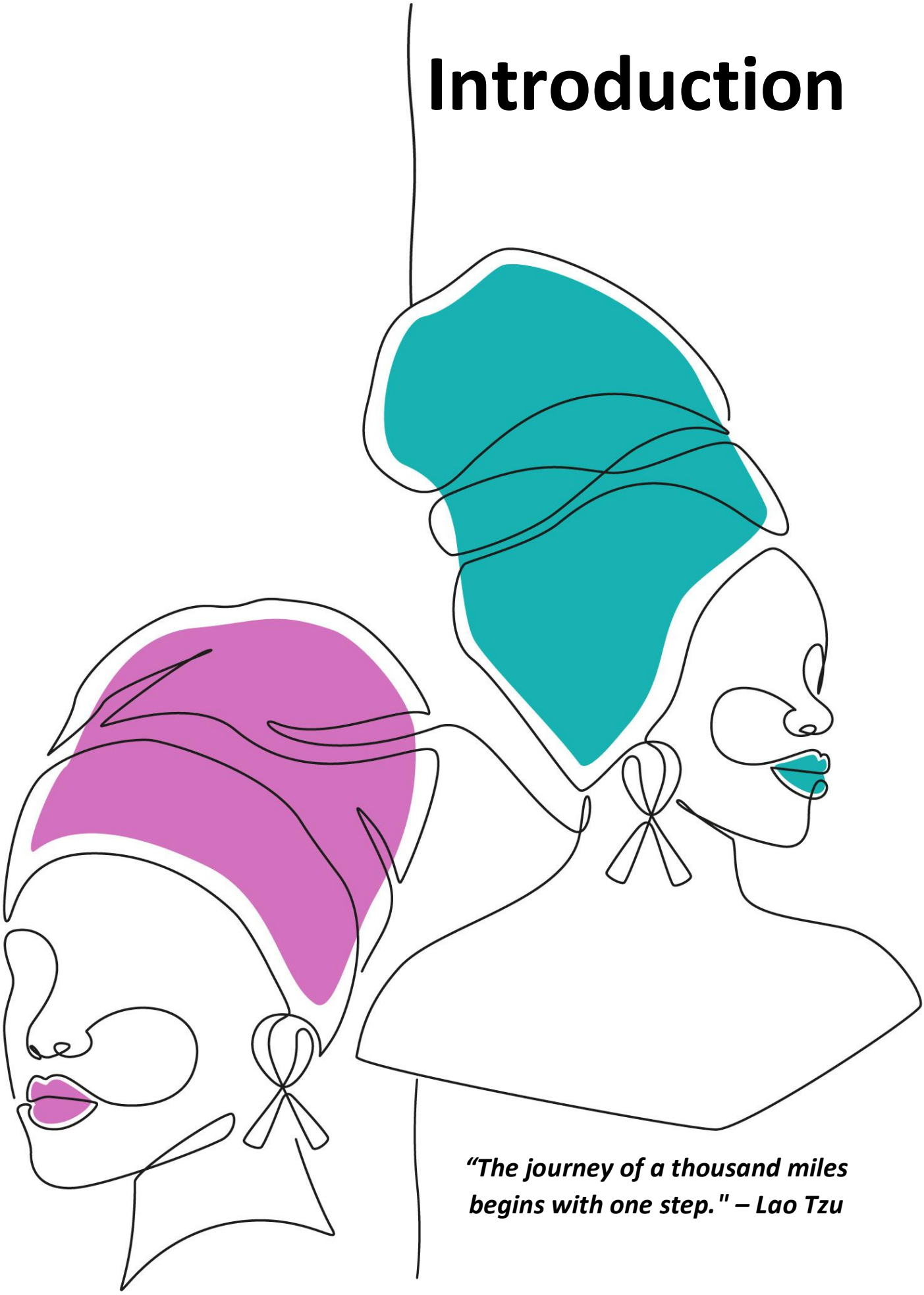
1. Dhokotera TG, Muchengeti M, **Davidović M**, Rohner E, Olago V, Egger M, Bohlius J. Gynaecologic and breast cancers in women living with HIV in South Africa: A record linkage study. International journal of cancer. 2024 Jan 15;154(2):284-96. https://doi.org/10.1002/ijc.34712
2. Ruffieux Y, Muchengeti M, Egger M, Efthimiou O, Bartels L, Olago V, **Davidović M**, Dhokotera T, Bohlius J, Singh E, Rohner E. Immunodeficiency and Cancer in 3.5 Million People Living with Human Immunodeficiency Virus: the South African HIV Cancer Match Study. Clinical infectious diseases. 2021 Aug 1;73(3):e735-44. https://doi.org/10.1093/cid/ciab087

Non peer reviewed publications

1. **Davidović M** and Bohlius J, on behalf of the IeDEA. Facility-based indicators to monitor cervical cancer control services for women living with HIV. R4d Policy Brief 2023, No. 1, [Internet], December 2023. Available at: https://k4d.ch/facility-based-indicators-to-monitor-cervical-cancer-control-services-for-women-living-with-hiv/
2. Asangbeh-Kerman SL, Katayoun T, **Davidović M**, Bohlius J. Indicators and targets for cervical cancer prevention in countries with the highest HIV burden: A scoping review protocol. AfricArXiv [Internet], April 2022. AfricArXiv [Internet]. 2022 Apr 14; Available from: https://africarxiv.pubpub.org/pub/argxh98c

The complete list of published articles I authored or co-authored is available in Chapter 8: COMPLETE LIST OF PUBLICATIONS.

Introduction



“The journey of a thousand miles begins with one step." – Lao Tzu

1. INTRODUCTION

In this chapter, I introduce the epidemiology of HIV, and of the two most common cancers in– cervical cancer and breast cancer – with a focus on women living with the human immunodeficiency virus (HIV) in sub-Saharan Africa. I summarize the risk factors for cervical and breast cancers and explain the role of the human papillomavirus (HPV) in the development of cervical cancer. Additionally, I present the Cancer Prevention and Care Continuum and elaborate on different steps in a comprehensive cancer prevention and care, with a focus on cervical and breast cancer, and women living with HIV. I also discuss the current recommendations for and the importance of integrating and monitoring cancer prevention and care services in sub-Saharan Africa.

1.1. HIV in sub-Saharan Africa

Sub-Saharan Africa remains the epicenter of the HIV pandemic; of the 7.5 million [31.8–43.6] adults (15 years or older) living with HIV worldwide, 67% reside in this region [1]. The epidemic is generalized (infection rates of >1%) in most countries, with some areas experiencing concentrated epidemics among key populations [1, 2]. The highest adult prevalence have been reported in Eswatini (26.5%), followed by South Africa (17.9%), Namibia (13.3%), and Mozambique (11.1%) [1]. The HIV pandemic disproportionately affects women – HIV prevalence among adolescent girls and young women is more than three times higher than among their male counterparts in this region [1]. Several factors, including biological, social, behavioral, cultural, economic, and structural, contribute to the disparate increase in HIV infection rates among women compared to man. Despite a 65% reduction in HIV incidence among women and girls since 2010, women and girls (of all ages) accounted for 63% of all new HIV infections in 2022 in this region [1]. The trends in new HIV infections vary by countries and regions, with the HIV incidence among adolescent girls and young women generally being the highest in Eastern and Southern Africa (Figure 1) [1].

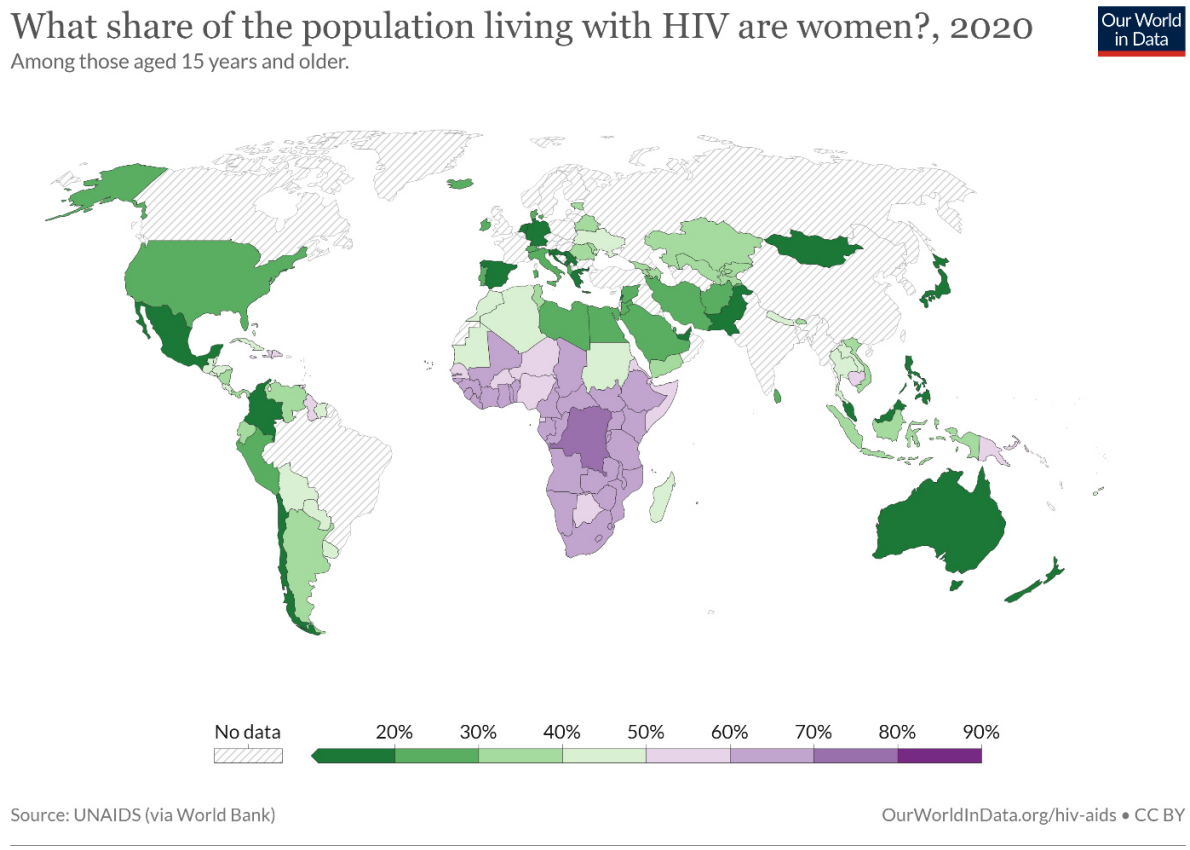


Figure 1. *The share of female population aged 15 years or older who are living with HIV, 2020. Adapted from Our World in Data website. By World Bank (2023). Retrieved from https://ourworldindata.org/grapher/share-of-women-among-the-population-living-with-hiv*

The HIV is a viral infection transmitted through exposure to infected semen, blood, vaginal and anal fluids, and breast milk. HIV attacks immune system cells, weakening the body's capacity to defend itself against infections. Specifically, the HIV targets CD4 cells, a type of white blood cells essential to fighting infections, and replicates within these cells. Each infected CD4 (a type of white blood cell) cell can produce hundreds of copies of new HIV particles. Over time, infected individuals become immunodeficient, making them vulnerable to opportunistic infections, infection-related cancers, or other chronic comorbidities that are rare in individuals with a healthy immune system [3]. CD4 cell counts are often measured to assess the individual's immune system status. The most advanced stage of HIV infection is Acquired Immunodeficiency Syndrome (AIDS), which typically takes several years to develop if the person is not diagnosed or treated with antiretroviral therapy (ART). An HIV RNA viral load test measures the amount of HIV RNA in the blood, and it monitors viral replication and effectiveness of the treatment, while a CD4 cell count test assesses

the person's immune status and the progression of HIV disease. The normal range for CD4 cell count is from 500 to 1500 cells/mm^3 of blood, and it progressively decreases over time in persons who are not receiving or not responding well to ART. HIV infection can be diagnosed using simple, affordable, and rapid diagnostic tests or self-tests, that offer same-day results and can be done at home. Nevertheless, a confirmatory laboratory test is necessary for a definitive diagnosis.

Individuals with HIV who are undergoing lifelong ART enjoy a long and healthy life.

After ART became available in sub-Saharan Africa in 2004, initially recommended only for those with very advanced immunodeficiency and HIV disease, access to treatment gradually expanded in sub-Saharan Africa [4]. In late 2015, the WHO further expanded their HIV treatment guidelines and recommended the "treat all" approach, offering ART to all individuals with HIV, regardless of CD4 cell count or clinical stage [4]. Once diagnosed with HIV, individuals should be promptly offered ART and periodically monitored using clinical and laboratory parameters. While ART does not cure HIV, it effectively suppresses viral replications and eliminates the risk of sexually transmitting the HIV. The treatment strengthens individual's immune system and its capacity to fight various infections, enabling individuals with HIV who adhere to lifelong ART to lead long and healthy lives. According to UNAIDS, around 88% of people living with HIV in sub-Saharan Africa knew their status in 2021, while 78.5% were receiving ART and only 71.5% had suppressed viral loads [1, 5]. In Eastern and Southern Africa, the proportions of people living with HIV who know their HIV status, who are on ART and who are virally suppressed are almost the same as in some high-income European and North American countries [1]. In the last decade, the annual number of new HIV infections in sub-Saharan Africa fell by almost 50% between 2010 and 2020, while AIDS-related deaths decreased by 47% over the same period [1]. Nevertheless, the reduction trends varies among regions. Eastern and Southern Africa have reported the largest decrease of annual new HIV infections compared to any other region, with a decline of 38% of new HIV infections since 2010. Great reductions in new HIV infections were also achieved in western and central Africa, with a 25% decrease since 2010 [6].

Over the last decade, significant political efforts have been made in the African region to fight HIV/AIDS, particularly in massively expending access to ART [7]. This has

markedly improved the life expectancy of people living with HIV [8]. As a result, individuals living with HIV are now facing an increased burden of non-communicable comorbidities, including various non-AIDS-defining cancers (NADCs) [9, 10].

1.2. Cancer in sub-Saharan Africa

Cancer represents a major public health problem in sub-Saharan Africa. The increasing cancer burden is primarily attributed to the aging population, population growth, as well as an increased risk of the disease due to shifting lifestyle and behavior patterns associated with social and economic transition in this region. In the next 20 years, it is estimated that the cancer incidence and mortality burden will rise more rapidly in Africa than in other world regions [11, 12]. Even if cancer incidence rates were to remain unchanged in this region, the cancer burden is expected to nearly double by 2040, due to population growth and ageing [11, 12]. This could result in 1.5 million new cancer cases and one million deaths, many of which can be prevented [13]. The growing cancer burden also affects population living with HIV. Since the introduction of ART, an increased risk of NADCs among people living with HIV, compared to the general population, has been observed in both developing and developed countries [14, 15]. It is well documented that co-infections with oncogenic viruses, specifically with HPV, Epstein-Barr virus, and hepatitis B and C virus, occur at higher rates among people living with HIV than in the general population [15, 16]. This can primarily be attributed to HIV-induced immunodeficiency and systemic inflammation, which compromises their ability to combat infections and control the growth of cancer-causing pathogens [17, 18]. Other HIV-associated factors that increase risk of specific cancers include low CD4 cell counts [17, 19] and advanced stage of HIV (AIDS) [15, 20]. Modifiable behavior risk factors, such as physical inactivity, unhealthy diet, and the harmful use of alcohol, as well as metabolic risk factors (which may lead to overweight/obesity) are on the rise in sub-Saharan African countries [21, 22]. Some of these factors, including smoking and alcohol consumption, have been more prevalent in populations living with HIV compared to general population [10, 23-25]. Cancer burden is further driven by cancer inequality—uneven distribution of resources and cancer inequity—unjust, avoidable differences in care or outcomes [26]. Social and economic inequalities, in education level, income, occupational status, culture, ethnicity, and living conditions also affects cancer morbidity and mortality [13, 27]. Socially and economically disadvantaged populations

have poorer prognosis and outcomes, as they are more likely to have preventable cancers diagnosed at a later stage. Moreover, they are more likely to have inadequate access to cancer treatment [13]. The increasing cancer burden in sub-Saharan Africa is overshadowed by limited resources and other health challenges, such as HIV/AIDS, malaria, and tuberculosis. Cancer receives a relatively low public health priority in this region, possible due to a lack of awareness among policymakers, the general public, and health institutions regarding the magnitude and economic impact of the current and anticipated cancer burden in the region [28].

In sub-Saharan Africa, breast cancer is the most common cancer in 28 of 48 countries, and cervical cancer in 19 of 48 countries [12]. In 2020, there were 186,598 [173,041 – 201,217] new cases of breast cancer and 117,316 [105,999 – 129,842] new cases of cervical cancer [11]. Cervical cancer is the leading form of cancer death among women in 27 countries, and breast cancer is the leading cause of death among women in 21 countries in sub-Saharan Africa [12] (Figure 2). In 2020, 85,787 [77,648 – 94,779] women died from breast cancer, and 76,745 [68,380 – 86,133] from cervical cancer [11]. In this region, the risk of a woman developing cancer by the age of 75 years is almost 14.1%, with breast cancer (4.1%) and cervical cancer (3.5%) responsible for half of this risk [12].Cancer also imposes a substantial burden on individuals, their families, communities, and healthcare systems [12]. In 2020, more than one third (35%) of all new maternal orphans due to cancer were in Africa. Almost half of the new maternal orphans were due to deaths from breast and cervical cancer [29].

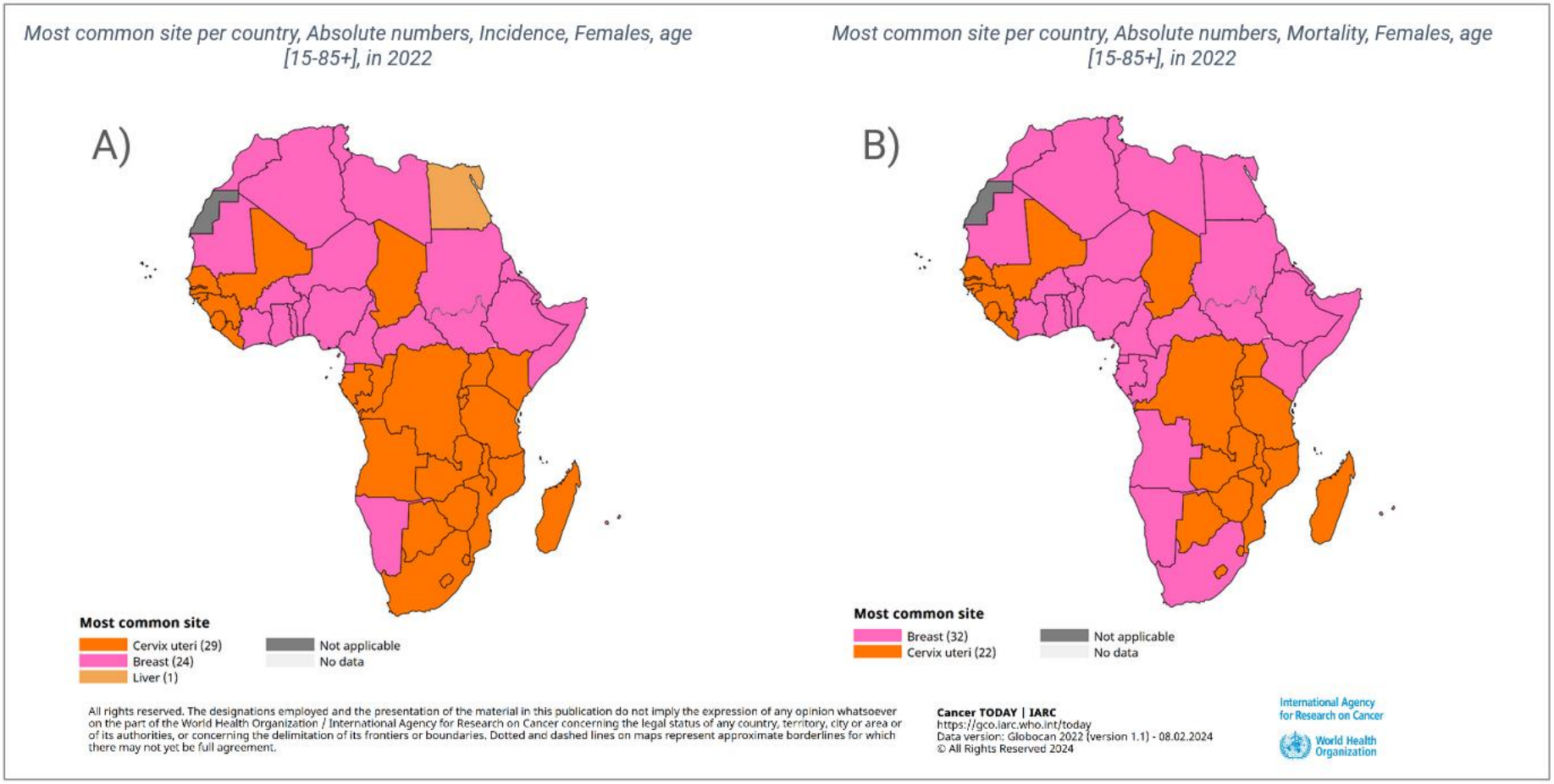


Figure 2. *The top cancer per country in sub-Saharan Africa in 2022.*

A) *Most common cancer (incidence) per country for female population aged 15 years or older;* ***B)*** *most common cancer (mortality) per country for female population aged 15 years or older. Adapted from Ferlay J et al (2020). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today, accessed 07 July 2024.*

1.2.1. Cervical cancer in sub-Saharan Africa

Sub-Saharan Africa records the highest incidence and mortality of cervical cancer globally [30, 31]. In 2020, age-standardized incidence rates of cervical cancer varied across regions, with eastern Africa experiencing the highest rates (40 cases per 100 000 women-years [95% CI 39·7–40·4]), followed by southern Africa (36·4 [35·8–37·1]), and Middle Africa (31·6 [31·1–32·1]) [30, 31]. Similarly, mortality rates differed regionally, with eastern Africa observing the highest mortality (28·6 deaths per 100 000 women-years [95% CI 28·3–28·9]) [31]. Nineteen of the top 20 countries with the highest cervical cancer burden in 2018 were located in sub-Saharan Africa [8], and this burden is expected to double by 2040 (Figure 3).

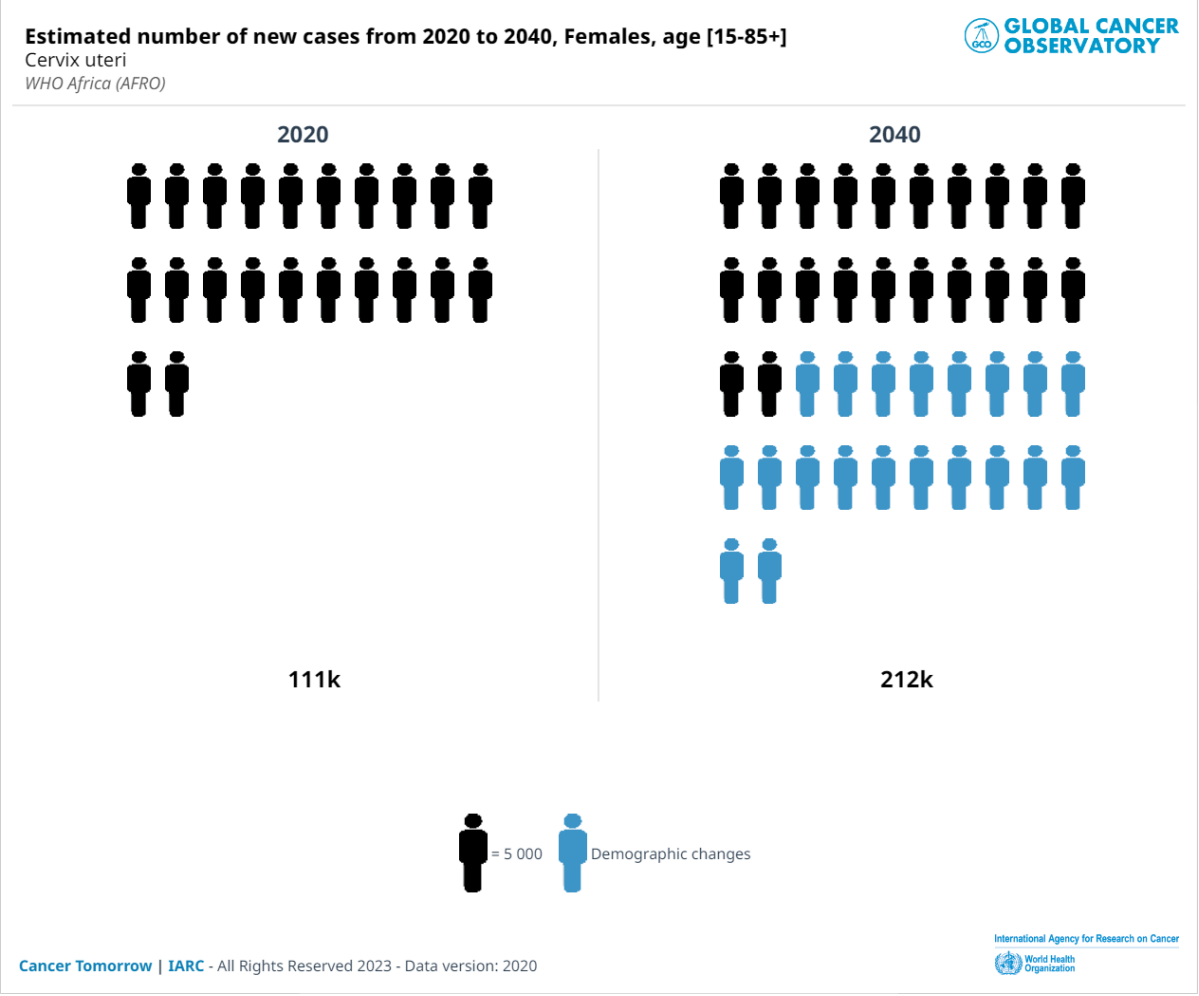


Figure 3. *Estimated number of new cervical cancer cases from 2020 to 2040 in female population aged 15 years or older in WHO Africa region. Adapted from Ferlay J et al (2020). Global Cancer Observatory: Cancer Tomorrow. Lyon, France: IARC. Available from: https://gco.iarc.fr/tomorrow, accessed 21 November 2023.*

Globally, there has been a notable decrease in both the cervical cancer incidence and mortality in the general population over the last three decades [31, 32]. This decline is largely attributed to improved socioeconomic conditions, enhanced prevention and screening interventions for cervical cancer, as well as a decrease in parity and the prevalence of sexually transmitted diseases [32]. However, significant global inequalities in cervical cancer incidence and mortality rates persist between high- and low-income countries. Countries with lower Human Development Index (HDI) experience significantly higher rates of cases and deaths compared to those with very high HDI [31]. Cervical cancer incidence is three times higher in countries with low HDI compared to those with very high HDI. This socioeconomic disparity is even more pronounced in mortality rates, which are six times higher in countries with low HDI compared to those with very high HDI [31]. The cervical cancer burden mirrors social and economic inequalities, and inequities in the prevention, diagnosis, and treatment of cervical cancer [26, 33]. Factors such as residence, geography, education level, wealth, health insurance status, and the health system capacity play an important role in determining access to cancer prevention and care services, thus influencing its incidence and mortality rates [33-36]. In sub-Saharan Africa, the high HIV and HPV prevalence, the limited availability, coverage, and quality of cancer prevention and care measures [37] contribute greatly to these drastic regional disparities.

Most cervical cancers are caused by certain HPV types, a widespread group of over 150 related viruses. HPV is commonly transmitted through skin-to-skin contact, including sexual activity. It is likely that most sexually active individuals will encounter HPV at some point, with the possibility of multiple infections [38]. For most persons (90%), the body's immune system will clear the infection. However, for some, the infection becomes chronic [38]. While some types of HPV cause genital warts and are considered low-risk for cancer, others are identified as high-risk (hrHPV, also called oncogenic) because of their strong association with various cancers, including cervical cancer [38]. Currently, 12 HPV types are categorized as high-risk (types 6, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59), with type 68 also being considered potentially oncogenic [38]. A persistent infection of the cervix with hrHPV types can lead to cervical intraepithelial neoplasia (CIN), which, if left untreated may progress to invasive cervical cancer [38, 39]. The progression from infection to cancer spans several years, giving an opportunity for early detection and treatment. HPV causes 95% of cervical

cancer cases if not treated [39]. Particularly, two hrHPV genotypes, 16 and 18, cause nearly half of all high-grade CIN cases and about 70% of all invasive cervical cancer cases worldwide [38, 39]. Certain sexual behavior can increase the risk of cervical cancer, most likely by increasing exposure to HPV. These include becoming sexually active at young age, having many sexual partners, or a sexual partner who is HPV infected [38]. In addition, having a weakened immune system or chlamydia infection, long-term use of oral contraceptives (birth control pills), young age at first full-term pregnancy and having multiple full-term pregnancies also increase risk for cervical cancer [38].

Cervical cancer in women living with HIV

Cervical cancer is an AIDS-defining illness and the most common cancer in women living with HIV [37]. Women living with HIV are six times more likely to develop cervical cancer than those without HIV [37], often receiving a diagnosis at a younger age [40]. The increased risk of cervical cancer in women living with HIV is likely multifactorial. They are more likely to acquire a hrHPV infection, and less likely to clear it than women without HIV. Women living with HIV, along with other immunocompromised women, are more likely to have persistent HPV infections and more rapid progression to cervical pre-cancer lesions and cancer. Furthermore, women living with HIV have a high rate of treatment failure and recurrence of cervical pre-cancer lesions [37, 41]. A prevalence of persistent HPV infection among women living with HIV ranges from 47% to 53%, nearly twice as high as in women without HIV [42]. Factors such as low CD4 cell counts, high HIV RNA viral loads, and older age were associated with increased invasive cervical cancer risk women living with HIV [19, 43, 44]. Additionally, advanced immunodeficiency is strongly associated with an increased risk of developing AIDS-defining cancers, including cervical cancer among women living with HIV [19, 43]. Globally, nearly 6% of new cervical cancer cases in 2018 occurred in women living with HIV, with 5% of all cases attributable to HIV infection [37, 45]. Of all women with cervical cancer and HIV globally, 85% live in sub-Saharan Africa, where 21% of all cervical cancer cases are attributable to HIV infection. The burden of HIV-attributable cervical cancer is particularly pronounced in younger women within the region [45].

1.2.2. Breast cancer in sub-Saharan Africa

In sub-Saharan Africa, breast cancer age-standardized incidence rate is 36.2 per 100,000 women per year, which is lower compared to other world regions. Within the region, breast cancer incidence rates vary by country and have generally been increasing over the past decade [46]. In 2020, breast cancer accounted for 27.3% of all new cancer cases in women [30], affecting over 129 000 women in sub-Saharan Africa [47]. More than half (58%) of breast cancer cases occurred in women under the age of 50 [48]. The number of new breast cancer cases is expected to double by 2040 (Figure 4), largely due to population growth and aging [49].

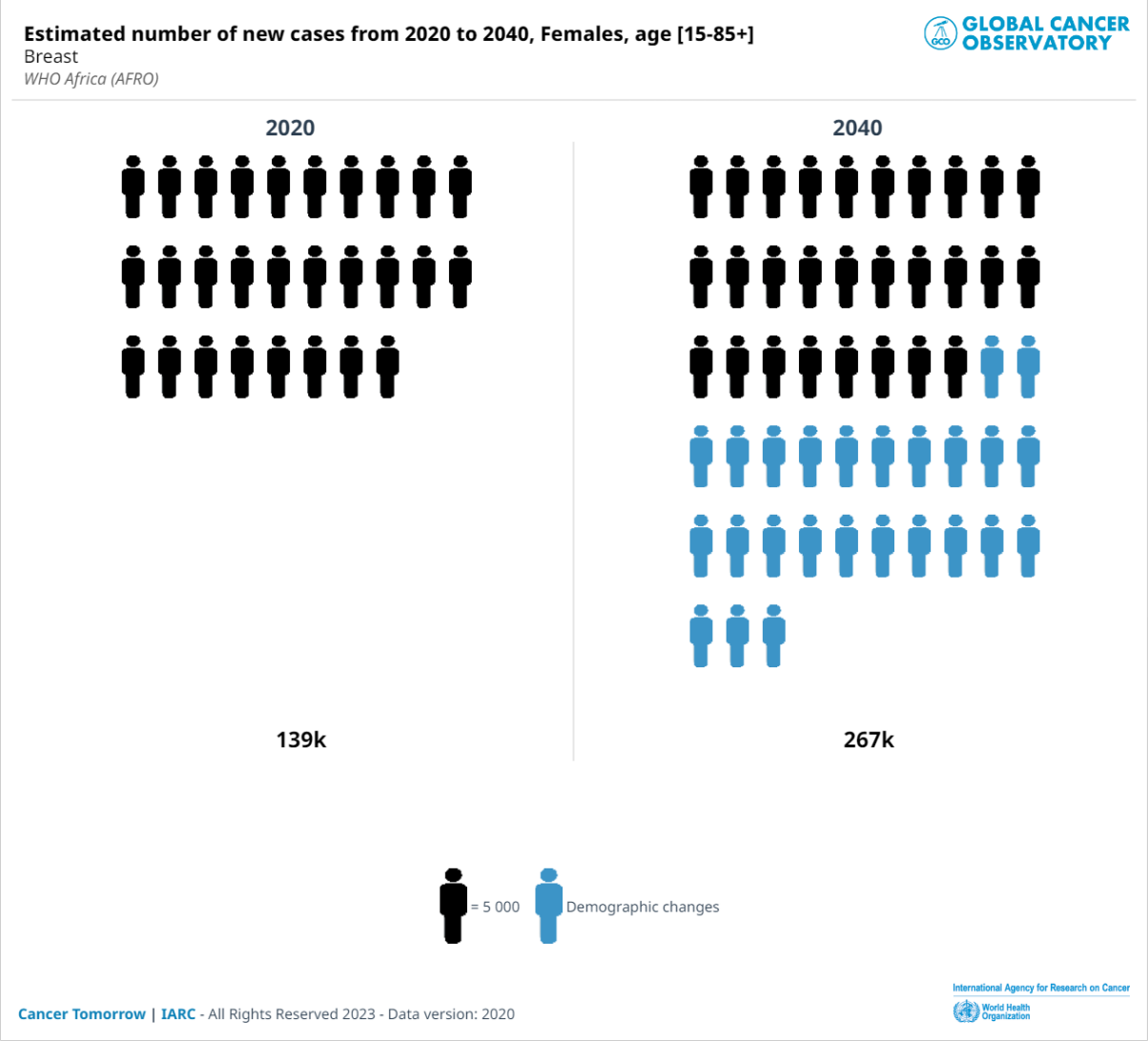


Figure 4. *Estimated number of new breast cancer cases from 2020 to 2040 in female population aged 15 years or older in WHO Africa region. Adapted from Ferlay J et al (2020). Global Cancer Observatory: Cancer Tomorrow. Lyon, France: IARC. Available from: https://gco.iarc.fr/tomorrow, accessed 21 November 2023.*

Breast cancer is a complex disease influenced by a multiple risk factors [50]. The strongest breast cancer risk factors are female sex and increasing age, with 99% of cases occurring in women and 1% in men [50, 51]. About half of breast cancer cases develop in women without any known risk factors beyond their gender and age (over 40 years) [50]. Additional key risk factors include genetics, such as a family history of breast cancer or mutations in BRCA or other genes, and hormone-and reproductive-related factors, such as late age at first pregnancy, nulliparity and low parity, little or no breast feeding, early onset of menses, late menopause, higher body mass index at postmenopausal ages, and prolonged exposure to elevated levels of sex hormones, oral contraceptive hormone therapy or postmenopausal hormone replacement therapy [50, 52, 53]. Other factors associated with an increased risk of breast cancer include environmental and lifestyle factors (low physical activity levels, high Body Mass Index (BMI), alcohol and tobacco consumption, certain exogenous hormone therapies), and breast-related factors as higher mammographic density and a history of proliferative benign breast conditions [50, 53]. The increasing breast cancer incidence in sub-Saharan Africa reflects demographics changes and the adoption of some above mentioned and lifestyle-, hormone-, and reproductive-related risk factors (commonly referred to as 'the effect of westernization') [22, 54]. This may be further exacerbated by increasing risk factors associated with globalization and a growing economy [30].

Breast cancer mortality rates have decreased by 40% in many high-income countries over the last three decades [50]. However, they remain high in the majority of low- and middle-income countries (LMICs). Sub-Saharan Africa has the highest breast cancer mortality rates worldwide, with half of all breast cancer deaths occurring in individuals under 50 years of age [50]. This high mortality rate is largely because many women in sub-Saharan Africa are diagnosed with breast cancer at an advanced stage [55]. Factors contributing to advanced disease include biological characteristics of the tumor, such as higher grade and triple-negative tumors. Furthermore, limited access to screening and early detection [22], as well as delays in diagnosis or starting treatment [56-58] in the region significantly affect the disease outcome [56]. Breast cancer mortality is further influenced by social factors, such as low educational and socioeconomic status, lack of awareness about the importance of early detection [50, 59], and a positive HIV status, with mortality rates being particularly high among Black women in this region [60].

Breast cancer in women living with HIV

There is no evidence for an association between HIV infection and breast cancer risk. However, the widespread use of ART, women living with HIV now live longer, reaching older ages at which the incidence of breast cancer is higher. This leads to a dual challenge of managing both breast cancer and HIV infection. Research on the association of HIV-induced immunodeficiency, ART and infection-unrelated cancers, including breast cancers [17, 19] is limited, especially with individual patient data from sub-Saharan Africa. In the South African nationwide cohort study I contributed to (see Supplementary Chapter 10.1), we observed that women living with HIV who were diagnosed with breast cancer had a lower median CD4 count at the baseline compared to women without cancer [17]. However, there was no evidence for an association of lower CD4 counts and an increased risk of breast cancer. Another study I was involved in (see Supplementary Chapter 10.1), analyzed over 3.4 million women in South Africa and investigated the incidence and risk factors for breast and gynecological cancers in women living with HIV [19]. The study has found a significant incidence of gynecological and breast cancers among these women. Older women living with HIV had an increased risk of developing breast cancer compared to younger women living with HIV. Low CD4 cell counts and high HIV RNA viral loads were associated with an increased risk for cervical and other HPV-related cancers, but not breast cancer [19]. There was some evidence of an increased risk of breast cancer in facilities of high compared to facilities of low municipal socioeconomic position [19].

The first global estimate on breast cancer among women living with HIV reported that the majority (70%) of these women were diagnosed with breast cancer before the age of 50 years, most between 35 and 49 years [61]. Women living with HIV tend to be younger at breast cancer diagnosis compared to women living without HIV [60, 62]. This reflects the generally younger age structure of the population living with HIV. In various African regions, the proportion of breast cancer patients under age 50 who were HIV positive ranged from 4-6% in Middle, Western, and Eastern Africa, to 26% in South Africa [61]. Breast cancer in women living with HIV is a complex issue that requires further investigation. Some studies have reported a similar or slightly lower risk [63, 64] or likelihood to have breast cancer [65] compared to population living without HIV. Despite limited evidence, studies suggest a potential link between HIV infection, ART, and a breast cancer risk [63-65]. Furthermore, survival rates from

breast cancer are lower in women living with HIV than those without [62]; however, survival is higher for women living with HIV on ART compared to those not receiving ART. This underscores the critical role of ART in improving cancer outcomes among women living with HIV. Despite uncertainty, HIV infection may influence the natural history and treatment of breast cancer and calls for a better understanding of the reasons underlying breast cancer care and outcome inequities in sub-Saharan Africa.

1.3. The cancer prevention and care continuum

The cancer prevention and care continuum is a framework used in public health and research to describe various steps from cancer etiology, prevention, early detection, diagnosis, treatment, survivorship, palliative care, and end-of-life [13, 66]. The framework covers a wide array of activities and interventions aimed at reducing the cancer incidence, morbidity, and mortality, while also improving the quality of life for cancer patients. In this thesis, I have applied this framework to develop a "cancer prevention and care continuum" (Figure 5), inspired by the widely used HIV treatment cascade and care continuum [67]. In the cancer prevention and care continuum, I refer to the dynamic and bidirectional navigation related to individual-level engagement in cancer prevention and care activities. Certain interventions or research topics may align with multiple steps along the continuum or span across the entire continuum. Nevertheless, this framework serves as a useful concept for understanding the comprehensive approach to the cancer elimination (refers to cervical cancer only) or cancer control. This holistic approach includes systematic implementation of evidence-based interventions for primary, secondary (screening and early diagnosis) and tertiary prevention (treatment, palliative care, and survivorship care) [68, 69]. The cancer prevention and care continuum supports in assessing plans and priorities, identifying research or practice opportunities and existing gaps. In my thesis, I will mainly concentrate on the prevention and care steps within the continuum, and I will not elaborate further on etiology of cancer or the aspects of palliate care and survivorship. Figure 5 presents the main aims of each level of cancer prevention and care strategies. In summary, primary prevention aims to reduce individuals' exposure to risk factors or to increase their resistance to them, and to prevent a cancer from beginning to develop [69]. Secondary prevention aims to find and ameliorate precancerous conditions or find cancers at early stages, when they can be treated more successfully. It aims to prevent the progression of the disease in an asymptomatic population (through screening) or at the detection of the first clinical symptoms (through early detection) [68, 69]. Tertiary prevention aims to reduce the impact of long-term disease and disability caused by cancer or its treatment, and to prevent cancer-related complications or cancer recurrence in cancer survivals [69].

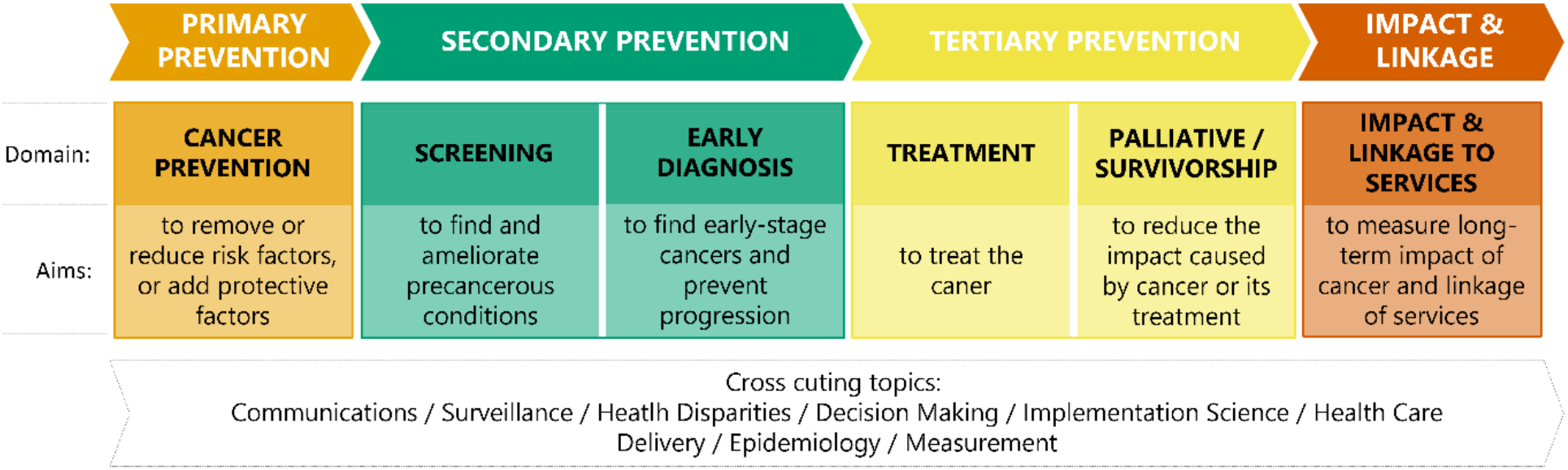


Figure 5. *The Cancer Prevention and Care Continuum. Adapted from David B. Abrams, Brown University School of Medicine, the National Cancer Institute, Division of Cancer Control & Population Sciences, and from handbooks of Cancer Prevention (2019) and Chambers A. David et al. Advancing the Science of Implementation across the Cancer Continuum (2018).*

Cancer control represents a long-term, high-value investment and is an integral part of the journey towards universal health coverage [13]. It requires a coordinated, multi-sectorial, and international effort from people and organizations through actions, policies, and services. To tackle the increasing burden of cancer in sub-Saharan Africa, it is essential for each country to implement a cancer control plan as part of its national health strategy and to establish or improve routine surveillance systems. These systems are crucial for monitoring progress in the delivery of specific cancer prevention and care interventions [12, 70]. To address these needs [70] and to support efforts [71] in collecting and evaluating indicators within the scope of global cancer surveillance, the WHO has set cervical cancer elimination and breast cancer control targets. These targets are designed to assess the ongoing scale-up of global initiatives on cervical and breast cancer [12, 39, 50]. My research and publication efforts align with and support these two WHO's global initiatives: the Cervical Cancer Elimination Initiative and the Global Breast Cancer Initiative (GBCI), which are further described in relevant sections.

Figure 6 outlines the major milestones achieved by both initiatives, along with recent WHO publications that have significantly contributed to this field. These publications are frequently referenced in the following chapters. Although these initiatives have a global scope, my specific focus in this thesis is on addressing the challenges and advancing knowledge related to cervical and breast cancer in the context of sub-Saharan Africa and among women living with HIV. In the subsequent sections, I will delve into the specifics of each prevention level by discussing specific cancers (cervical and breast cancers) and their corresponding prevention and care strategies.

Despite the progress achieved through these global initiatives, a considerable gaps persist in the prevention and care of cervical and breast cancer in sub-Saharan Africa, particularly in women living with HIV. This gap is characterized by the absence of comprehensive policies and programs specifically tailored to women living with HIV, insufficient reliable and standardized data to guide these efforts, limited resources for programs implementation, and inadequate coordination among stakeholders involved in cancer prevention and care [28, 72]. These obstacles hinder the progress towards cervical cancer elimination and breast cancer control in sub-Saharan Africa, highlighting the critical need for targeted efforts for women living with HIV to overcome these challenges, which my research aims to address.

Figure 6. *World Health Organization' milestones and cervical and breast cancer control publications relevant for my research. Images are retrieved from https://www.who.int/publications*

1.3.1. Cervical cancer prevention and care continuum

Cervical cancer is largely preventable through both HPV vaccination and screening for cervical pre-cancer, with appropriate follow-up and treatment [73]. It can be eliminated as a public health problem with comprehensive prevention and care measures combined with efforts to address social, health, and other inequalities. In 2020, The WHO launched the **global strategy to eliminate cervical cancer** as a public health problem. The aim of this strategy is to reach and maintain cervical cancer incidence rate below four per 100,000 women-years per country within a century. According to modeling studies, achieving this goal might be possible if all countries meet the WHO '90-70-90' targets by 2030: 90% of girls are fully vaccinated with the HPV vaccine by the age of 15 years; 70% of women are screened using a high-performance test, such as the HPV test, by the age of 35 years, and again by the age of 45 years; 90% of women diagnosed with cervical disease receive appropriate treatment [39, 74]. Achieving this goal would avert over 62 million of cervical cancer deaths cumulatively by 2120 in low- and lower-middle-income countries [39, 75].

The modelling study shows that girls-only HPV vaccination would lead to cervical cancer elimination in most LMICs, if high coverage is reached and the vaccine provides long-term protection [76]. However, countries with the highest cervical cancer burden, more than 90% of which are in sub-Saharan Africa, would not reach elimination by HPV vaccination alone [76]. To eliminate cervical cancer in these countries, high participation in cervical screening will be essential [76]. Well organized cervical screening programs have been shown to reduce the cervical cancer incidence of and mortality at the population level over time [77]. In such screening programs, it is important to ensure not only high coverage of the target population, but also that women who screen positive are linked to timely and appropriate treatment. Several, mostly high-income countries have been shown remarkable progress towards cervical cancer elimination and are close to meeting, or even surpassing, the WHO targets by 2030 [78]. However, progress in LMICs on HPV vaccination, screening and treatment is lagging behind [78, 79].

The global reductions in cervical cancer incidence and mortality is only achievable through a multi-sectoral and integrated approach across the continuum of cancer prevention and care [75, 76]. The WHO strategy recommends interventions at primary,

secondary, and tertiary prevention level and includes multidisciplinary approaches and components across the life course (Figure 7).

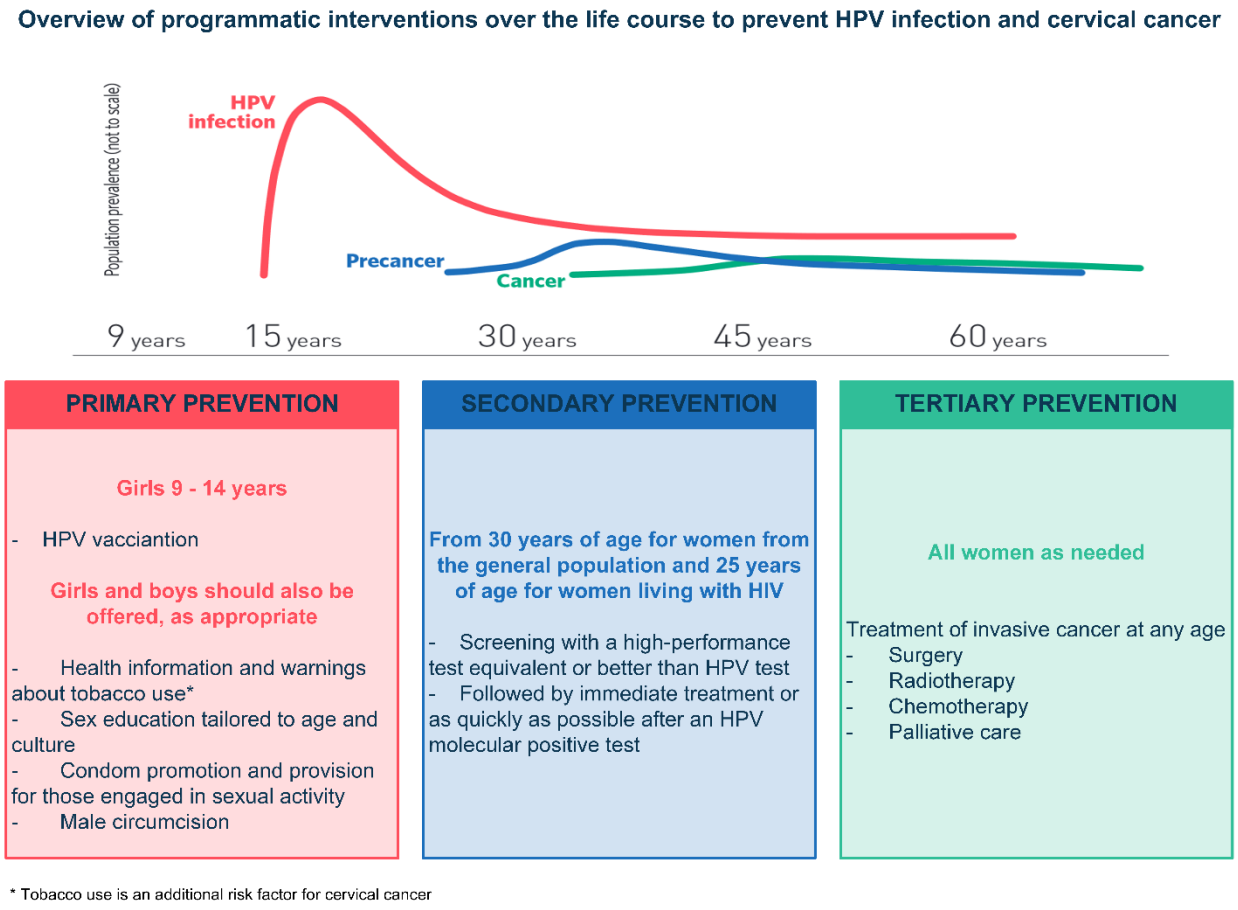


Figure 7. *Overview of programmatic interventions over the life course to prevent HPV infection and cervical cancer. Adapted from WHO Global strategy to accelerate the elimination of cervical cancer as a public health problem (2020).*

As a **primary prevention**, WHO recommends the HPV vaccination [80] that is highly effective in preventing HPV infections, high grade pre-cancerous lesions and cervical cancer. WHO recommends vaccinating girls aged 9 to 14 years, when most have not started sexual activity, and yet not being exposed to HPV. Vaccination is also advised for pre-adolescent boys and young adults who have not previously been vaccinated, whenever feasible. Currently, there are four types of HPV vaccination that have been prequalified by WHO, and all protect against hrHPV types 16 and 18. HPV vaccine has excellent safety profile – more than 350 million doses have been administrated globally by 2020 [81]. Individuals known to be immunocompromised or HIV-infected (regardless of age or ART status) should receive at least two HPV vaccine doses (minimum 6 months interval) and, where possible, three doses [82]. Although the HPV

vaccine is the most effective intervention to prevent cervical cancer, other important measures include promoting and providing condoms, encouraging safe sexual practices and male circumcision, health education, raising awareness about cervical cancer and its causes and risk factors, and advocating for tobacco abstention or cessation [3, 83]. **Secondary Prevention** refers to screening and treatment of cervical pre-cancer lesions. There are two major approaches to cervical screening and treatment 1) the screen-and-treat approach and 2) screen, triage, and treat approach [84]. In the first one, the decision to treat is based on a positive primary screening test only, without histological diagnosis. The aim is to destroy or remove the transformation zone of the cervix, or remove areas of the cervix that have been identified as abnormal by screening [84]. In the second one, the decision to treat is based on a positive primary screening test followed by a positive second test (a triage test), with or without histologically confirmed diagnosis [84]. Cervical screening tests aim to detect HPV infection or cervical pre-cancer lesions that can be treated (Table 1).

Table 1. *Cervical screening tests*

Molecular tests	Cytologic tests	Visual inspection
Aim: to detect HPV virus	**Aim: to detect abnormal cells**	
Nucleic acid amplification tests (NAAT)[a] – High risk HPV DNA/NAAT – mRNA **DNA methylation[b]** **Biomarkers[b]** – HPV antibodies – Oncoproteins	**Conventional Pap smear[a]** **Liquid-based cytology (LBC)[a]** **Dual staining to identify p16 and Ki-67[a]**	**Visual inspection with acetic acid or with Lugol's iodine (VIA/VILI)[a]** – Naked eye – Magnified by coloposcope or camera **Automated visual evaluation of digital images[b]**

[a] Current tests; [b] Tests under evaluation

Adapted based on WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, 2nd edition. Geneva: World Health Organization; 2021.

Cytology tests (Regular Papanicolaou [Pap] tests, also known as Pap Smears) are widely used to detect precancerous changes in cervical cells, allowing for timely intervention and treatment. When the results are positive, the diagnosis is confirmed by colposcopy with biopsy if indicated, and histological diagnosis to further decide on appropriate treatment [84]. Effective cytology-based cervical screening programs have drastically reduced cervical cancer mortality in some countries in the last 50 years, but it requires a good laboratory infrastructure. Another widely used screening method is

Visual Inspection with Acetic Acid (VIA) or with **Lugol's iodine** (VILI) via naked eyes or magnified by colposcopy or camera. These methods involve applying a dilute solution of acetic acid or Lugol's iodine to the cervix and visually inspecting the changes. The acetic acid causes abnormal precancerous or cancerous cells to turn white (acetowhite), while Lugol's iodine stains normal cells dark brown and leaves abnormal cells unstained or lightly colored, making them easier to identify [84]. These are low-cost, effective screening methods, especially useful in low-resource settings. They can be further advanced with complementary techniques as using digital cameras or smartphones to capture images of the cervix after application of acetic acid or Lugol's iodine, or portable colposcopy that are smaller, more affordable, and easier to use than traditional colposcopies [84]. **HPV Testing** aims to identify hrHPV strains that are linked to cervical cancer, and is suitable to use in various settings. The tests are broadly classified as those that detect HPV DNA, tests that identify messenger HPV RNA, and nucleic acid amplification tests that detect HPV. These tests either detect the presence of any of the 12 hrHPV types, or presence of any of these HPV types in the sample without individually identifying the genotypes, or detect a limited number of genotypes (mostly types 16 and 18) concurrently, with aggregate detection of the other hrHPV genotypes [84]. Recently some **novel screening methods** have been developed, as other molecular tests to detect HPV, objective tests performed on cytological samples, and advanced visual inspections tests based on artificial intelligence and machine learning platforms [84].

Integral goal of the secondary prevention is **the treatment of cervical pre-cancer lesions:** an removal of the epithelial transformation zone including the lesion, typically in an outpatient setting [85]. The methods of treatment may be ablative (destroying abnormal tissue by heating it with thermal coagulation or freezing it with cryotherapy) or excisional (surgically removing abnormal tissue). Ablative treatments do not result in a tissue specimen for histological evaluation [84]. Cryotherapy is the most common method for treatment of cervical pre-cancer lesions, as it can be performed without anesthesia at all levels of the health system. While ablation is effective for most cervical pre-cancer lesions, some cases, such as extensive lesions or suspicion of advanced cervical pre-cancer lesions will require excision [85]. Most commonly used excisional technique is Large Loop Excision of the Transformation Zone (LLETZ) and cold knife conization (CKC) [84, 85]. **Tertiary Prevention** refers to invasive cervical

cancer treatment, follow-up, and palliative pare. If cervical cancer is diagnosed, appropriate treatment options such as surgery, radiation therapy, chemotherapy, or targeted therapy are implemented to remove or destroy cancerous cells [84]. Regular follow-up care is crucial to monitor for recurrence and manage any potential side effects of treatment. In cases where disease is advanced or incurable, palliative care focuses on improving the patient's quality of life by managing symptoms and providing psychological support.

The WHO recommends using HPV DNA detection as the primary screening test rather than VIA or cytology for both women living without or with HIV [39, 84]. For general population of women, WHO recommends to start screening at age 30 years, using HPV DNA detection in a screen-and-treat or screen-triage-treat approach with regular screening every five to ten years (Figure 8).

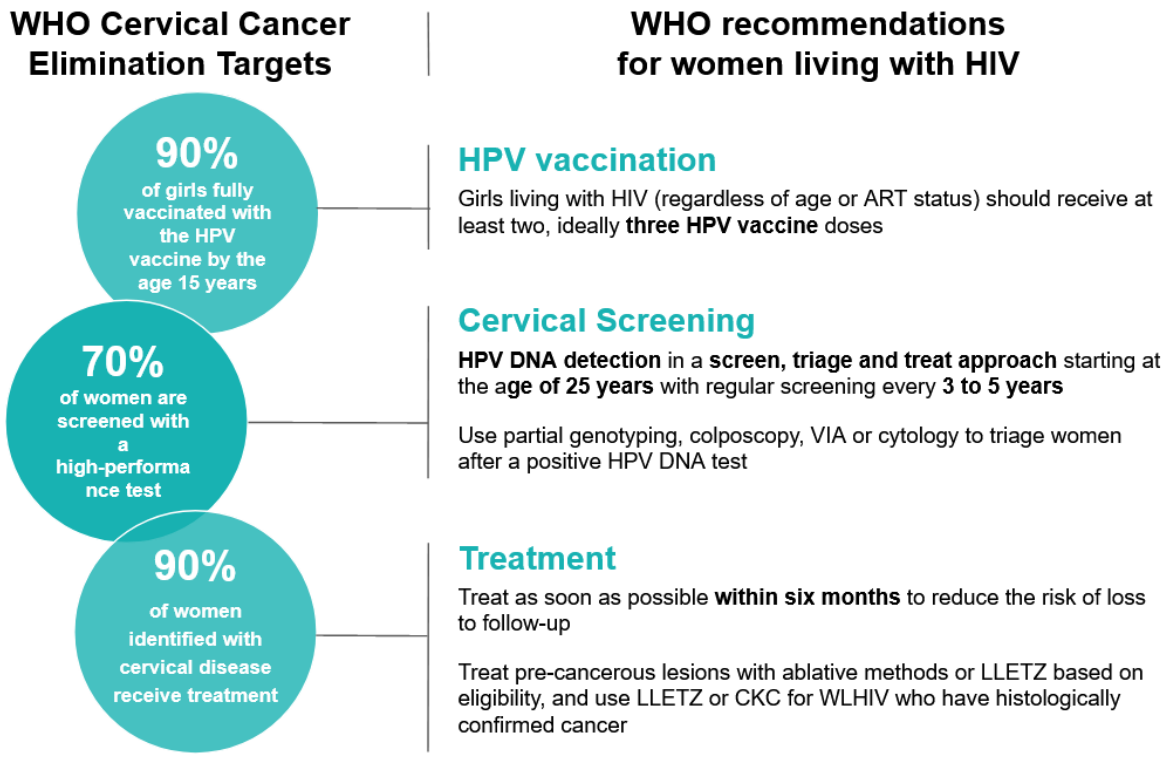


Figure 8. *WHO cervical cancer elimination targets for general population and recommendations for population living with HIV. Adapted and modified from WHO Global strategy to accelerate the elimination of cervical cancer as a public health problem (2020) and WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, 2nd edition (2021).*

For **women living with** HIV, the WHO recommends to start screening at age 25 years, using HPV DNA testing followed by a triage test (either cytology, VIA, HPV genotyping, or colposcopy) after a positive HPV DNA test [39, 84]. There is evidence that HPV

tests are superior to cervical cytology (Pap smear) or VIA in detecting cervical precancer and cancer in general population [86] and in LMICs [87]. Recent studies suggest that these tests are also effective in women living with HIV [88, 89]. However, another study assessing the accuracy of screening tests that can be used in low-resource settings and give results at the same visit, found that standalone hrHPV, VIA, and portable colposcopy testing missed almost a quarter (22.8%) of cervical pre-cancer lesions in women living with HIV with histologically confirmed advanced precancerous lesions (CIN2+)[90]. In that study, the sensitivity of HPV testing to identify CIN2+ was 67.3% (95% CI 57.7-75.7) and the specificity 65.3% (95% CI 59.4-70.7)[90]. Combing tests improved specificity but not overall accuracy of the tests. The choice of an optimal test, algorithms, and screening intervals for cervical screening and treatment often relies on weighing the benefits against potential harms [73], recognizing that, as of now, no test is perfect and inaccuracies, such as false positive and false negative results, can occur even in high-performing programs.

If women living with HIV are screened negative on both primary and triage tests, they should be re-screened every 3-5 years. Studies have shown that this approach leads to the most efficient reductions in cervical cancer incidence and mortality while also minimizing harms [88]. Women living with HIV who were screened positive on an HPV DNA primary test but negative on a triage test should be retested with HPV DNA testing in 12 months. If this subsequent test is negative, they should then follow the recommended screening intervals. The WHO also suggests that programs that are currently offering cytology as a primary screening test should continue until HPV DNA testing becomes operational. However, programs using VIA as the primary screening test should transition rapidly due to the challenges of assuring quality in VIA tests, particularly in women living with HIV. If screening detects abnormal cells or pre-cancer lesions, prompt medical interventions, such as colposcopy, biopsy, or loop electrosurgical excision procedure (LEEP), should be performed to remove or treat the affected tissue in both the general population and among women living with HIV, ideally within six months. Women living with HIV treated for cervical pre-cancer lesions should be retested in 12 months, where available. If the test is negative, a follow-up test should occur in another 12 months. Women who have histologically confirmed adenocarcinoma in situ, WHO suggests LLETZ or CKC, regardless of HIV status.

1.3.2. Breast cancer prevention and care continuum

When breast cancer is detected and treated early, the chances of survival are very high [91]. Breast cancer prevention and care comprise an organized set of activities aimed at preventing or reducing morbidity and mortality from breast cancer [92]. **Primary prevention** focuses on reducing the risk of developing breast cancer and enhancing protective factors. These measures include risk-associated lifestyle modification programs, chemopreventive medications like tamoxifen for women at moderate to high risk, and preventive surgery for those at highest risk, following thorough counseling and genetic testing [93]. Given the limited availability of genetic testing, particularly in sub-Saharan Africa, focusing on lifestyle improvements, such as promoting physical activity and healthier diets, along with raising awareness is crucial in preventing a substantial number of breast cancers [53, 94]. Effective strategies for include community outreach, media campaigns, and legislative efforts to educate the public, and are a feasible approach to improving early detection of breast cancer [95, 96]. **Secondary prevention** emphasizes early detection and screening to identify breast cancer at initial stage, where treatment is more likely to be successful. The aim of early detection is to reduce mortality by downstaging the disease at diagnosis – reducing the high percentage of late-stage presentation. This can be done either through the early clinical diagnosis of symptomatic breast cancer or by screening asymptomatic women [92]. Strategies for secondary prevention include regular screening methods such as mammography, clinical breast examination, and breast self-examination. Additionally, genetic testing may be advised for individuals at high risk due to family history or genetic predispositions, including mutations in the BRCA1 or BRCA2 genes. **Tertiary prevention** focuses on reducing the impact of the disease after it has been diagnosed, aiming to prevent progression and recurrence of metastasis, improve quality of life, and reduce symptom severity. It involves the management and treatment of women with breast cancer to minimize physical, emotional, and social complications.

In resource-poor settings, many women with breast cancer are diagnosed at a later stage, presenting with locally advanced or metastatic disease [91, 97]. Recognizing this challenge, the WHO established the **Global Breast Cancer Initiative (GBCI)** in 2021. The objective of the GBCI is to reduce global breast cancer mortality by 2.5% per year, aiming to avert 2.5 million breast cancer deaths globally between 2020 and

2040 [50]. I had the privilege of contributing to the development of the GBCI Implementation Framework [50], which offers evidence-based recommendations for improving early detection, diagnosis, treatment and supportive services. This framework outlines how to enhance systems for detecting, diagnosing, and treating breast cancer, proposing three key strategies for achieving these goals: health promotion and early detection, timely diagnosis, and comprehensive breast cancer management. In line with these three pillars, the identification of any system gaps can be facilitated through three evidence-based key performance indicators (KPIs) (Figure 9). To ultimately achieve the mortality reduction target of 2.5% per year set by the GBCI, it is crucial to implement actions across the breast cancer control continuum that meet the KPIs of all three pillars.

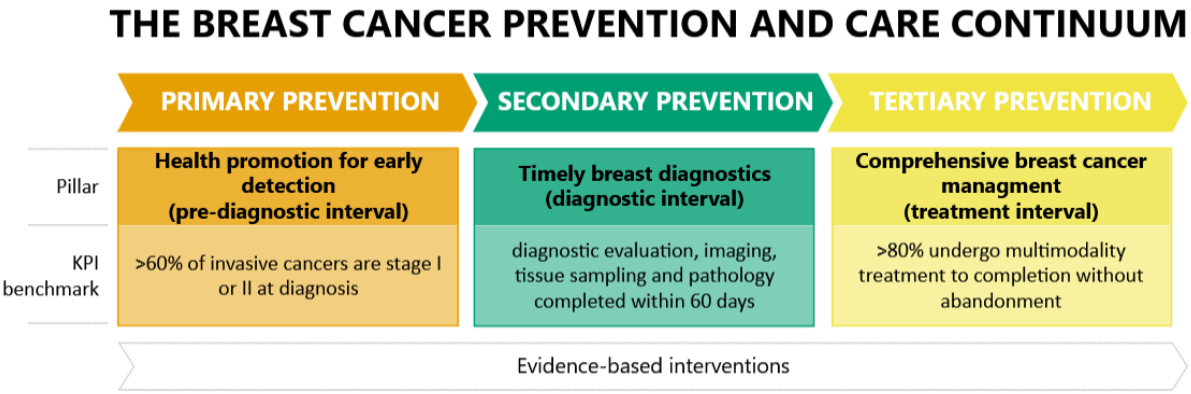


Figure 9. *The breast cancer prevention and care continuum. Adapted based on Global Breast Cancer Initiative (GBCI) Framework.*

Despite the well-established framework for breast cancer control, the practical application and effectiveness of these strategies significantly vary across regions, especially in LMICs. One of the key challenges in successfully implementing breast cancer control programs in resource-limited settings is the capacity for effective management of clinically identified breast cancer cases [91]. This includes ensuring that diagnostic services are widely accessible to offer timely and accurate diagnoses, which must be promptly followed by appropriate treatment. Addressing these challenges requires innovative and integrated approaches. Specifically, fostering international collaborations and leveraging current available infrastructure, e.g. offering breast cancer education, screening, and diagnosis at HIV clinics, can provide a cost-effective solution.

1.4. Integration and monitoring of cancer prevention and care services

Prioritizing an integrated approach to prevention, screening, and treatment services for cervical and breast cancer is crucial for efficiently reaching and supporting women at significant risk [39, 98]. Some healthcare systems are adapting to meet the growing needs of an aging population living with HIV by integrating cancer prevention and care services with HIV support [1]. Service integration supports health system to be more people-centered and context-specific, making services more optimal and easy to navigate [1]. Integrating cancer and HIV services using alternative models of service delivery has been proven to be cost-effective [99], feasible, and acceptable, especially for women living with HIV [100]. Integration methods include using the same internal staff within a clinic, co-locating services within the same facility, or through more complex integration and coordination programs. These approaches can be enriched with patient navigation programs that have been shown to be effective in addressing the fear and stigma, and overcoming system barriers [101, 102]. Furthermore, leveraging existing infrastructure, like the widespread network of HIV clinics in sub-Saharan Africa and partnerships like the IeDEA collaboration [103], can help improving the uptake of cancer prevention and care services for women living with HIV and ultimately prevent and improve cancer outcomes [37, 98].

To enhance cancer prevention and care for women living with HIV in sub-Saharan Africa, we need accurate and up-to-date information on the cancer service availability, facility capacity and readiness to deliver these services, and the service quality [72]. Monitoring is the process of systematically collecting data to measure the achievements of the program or activity, which are assessed periodically, using a set of measurable indicators. Resulting information are used to inform stakeholders, program managers, and policy-makers, facilitating strategic decisions for program management and quality enhancement. Both WHO global initiatives, the Global Strategy to eliminate cervical cancer and the GBCI emphasize monitoring and evaluation as a priority action to strengthen health systems. Regular assessments using a set of measurable indicators may generate reliable data on cancer prevention and care program performance, aiding in better decision-making [39, 50]. Data harmonization and aggregation play an important role in making collected data during health care delivery meaningful [66].

Despite established strategies for cancer monitoring and evaluation, countries in sub-Saharan Africa face challenges in implementation, standardization, and collecting high-quality data [70, 72]. Data collection is often inconsistent and unstandardized, focused on research or specific programs rather than being routinely collected across sites or tailored to the key population. Some of the current challenges in routine health facility data collection include the lack of standardized set of data elements and indicators, missing data types, fragmented and duplicated data systems, poor data quality, and capacity gaps in data analysis, presentation, interpretation, and dissemination [104]. In regions with a high HIV burden, incorporating HIV status into routine data collection is crucial. Such a measure would be essential for monitoring the progress towards achieving the goals of the previously mentioned WHO initiatives for women living with HIV, and informing next targeted interventions to improve health outcomes [72, 98, 105].

Cancer data can be collected from various sources, including population-based surveys, cancer registries, hospital or program databases, facility-based surveys, or research by consortia and networks [72]. Among these, population-based registries are the most reliable source for determining cancer incidence rates, crucial for cancer control program planning and evaluation [12, 106]. However, in sub-Saharan Africa, despite recent increases in such registries driven by international support like that from the IARC, over 20 countries still lack adequate cancer surveillance due to funding shortages, lack of institutional commitment, inadequate training, underreporting, underdiagnoses, and poor data quality [12, 28, 106]. Addressing these challenges requires pooling and analyzing data from multiple sources to improve cancer policies and programs [72]. The effectiveness of these data integration methods, however, varies by country based on data collection and identification practices [107].

To effectively support women living with HIV, monitoring efforts must be intentionally designed to capture and address the specific challenges and disparities they face in accessing cancer prevention and care. There is an urgent need for focused research to develop targeted interventions and monitoring practices to improve health outcomes for women living with HIV and cancer in sub-Saharan Africa.

2. GENERAL AIMS OF THE THESIS

"There are many paths to the top of the mountain, but the view is always the same." – Chinese Proverb"

The overall aim of my thesis was to study cervical cancer and breast cancer, the two most prevalent cancers among women living with HIV in sub-Saharan Africa. The presented publications are intended to contribute to the elimination of cervical cancer and the control of breast cancer, specifically focusing on enhancing scientific evidence for women living with HIV. My objectives were to describe current policies (**Publication 3**), assess program practices and outcomes across the cervical cancer prevention and care continuum (**Publication 2**), and develop a tool for improving data collection on cervical cancer prevention and care programs with a focus on women living with HIV in sub-Saharan Africa (**Publication 1**). Additionally, I aimed to understand and describe the epidemiology of breast cancers in women living with and without HIV in South Africa (**Publication 4**).

My core research question was: **How can we contribute towards the elimination of cervical cancer and the control of breast cancer in women living with HIV in sub-Saharan Africa?**

More specific questions that needed to be addressed and objectives of each publication are listed below.

2.1. Publication 1

Facility-based indicators to manage and scale up cervical cancer prevention and care services for women living with HIV in sub-Saharan Africa: a three-round online Delphi consensus method

- How can we identify gaps in the cervical cancer prevention and care continuum for girls and women living with HIV in sub-Saharan Africa?
- How can we harmonize monitoring efforts at HIV clinics and scale up cervical cancer prevention and care programs offered to girls and women living with HIV in sub-Saharan Africa?
- How can we integrate variables needed to inform monitoring indicators into routine data collection practices at HIV clinics in sub-Saharan Africa?

Objective: to reach a consensus on facility-based indicators to monitor, manage, and scale up the cervical cancer prevention and care services offered to girls and women attending HIV clinics in sub-Saharan Africa.

2.2. Publication 2

Cervical cancer prevention in countries with the highest HIV prevalence: a review of policies

- What performance and result indicators are recommended for cervical cancer control in sub-Saharan African countries with the highest HIV prevalence?
    a. How are these indicators defined?
    b. How do these indicators and their definitions align with the core indicators recommended by WHO for program monitoring?
- What targets are defined for HPV vaccination, cervical screening, and treatment of cervical pre-cancer lesions and invasive cancer in sub-Saharan Africa?
- What are the tools available for program monitoring and evaluation in sub-Saharan Africa?
- What aspects and specific considerations of cervical cancer control for women living with HIV are defined in identified policies?

Objectives: to review policies and recommendations for cervical cancer control in sub-Saharan Africa, with focus on countries with high HIV prevalence, and to extract and describe indicators and standards used to monitor the programs.

2.3. Publication 3

Cervical cancer prevention and care in HIV clinics across Sub-Saharan Africa: results from a facility-based survey

- Which cervical cancer prevention and care services are currently available to and utilized by girls and women living with HIV attending HIV clinics in sub-Saharan Africa?
- How many girls are vaccinated against HPV, how many women are screened, screened positive, and treated for cervical pre-cancer lesions or cervical cancer at selected HIV clinics across sub-Saharan Africa?

- What patient-level data are currently available to monitor steps in cervical cancer prevention and care continuum for girls and women attending HIV clinics that offer either on-site or off-site cervical cancer prevention and care services in sub-Saharan Africa?

Objectives: to qualitatively assess the implementation of cervical cancer prevention and care services at the facility level, and to utilized patient-level data to populate the steps across the cervical cancer prevention and care continuum for women living with HIV attending HIV clinics with fairly evolved cervical cancer prevention programs across sub-Saharan Africa.

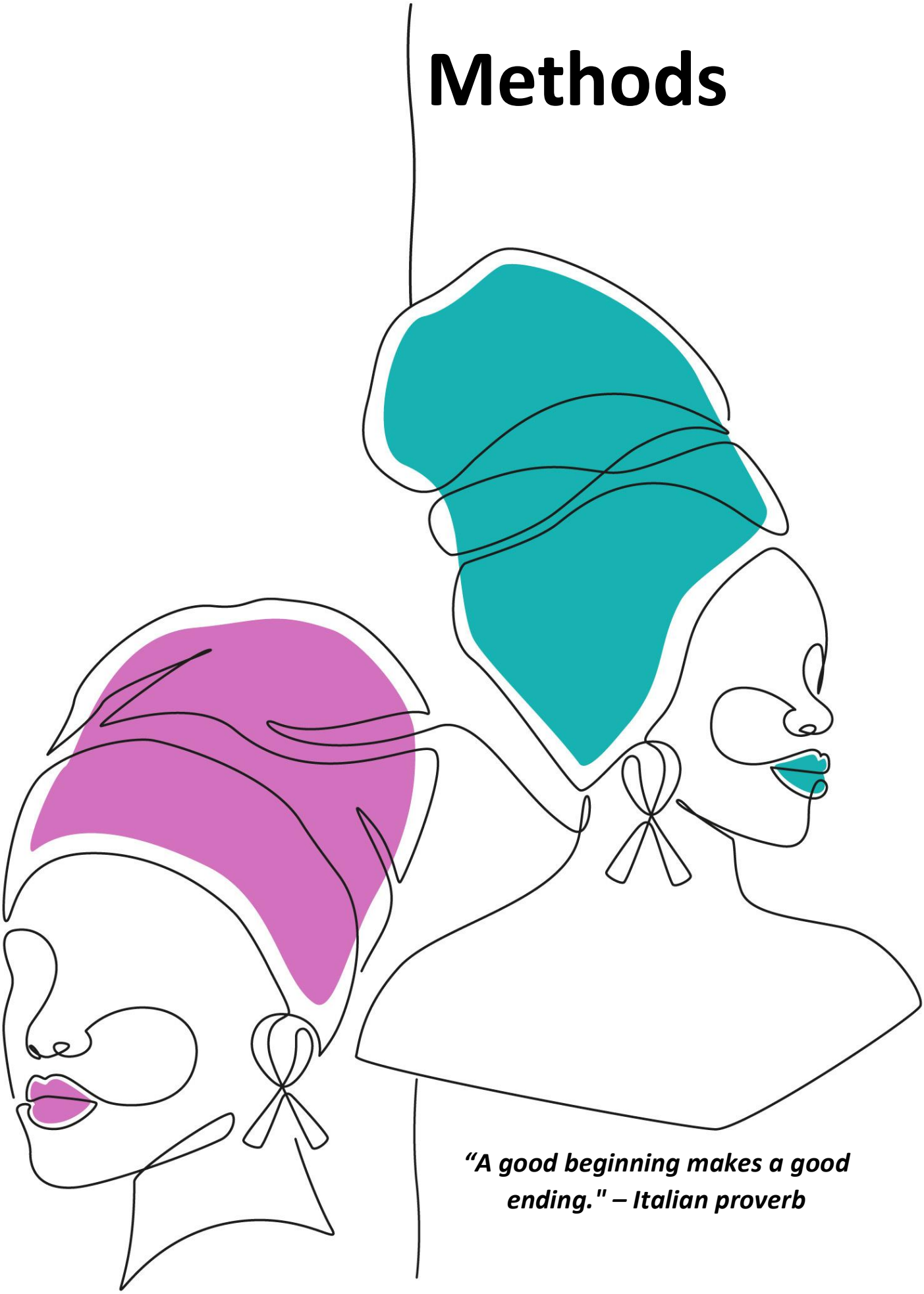
2.4. Publication 4

Breast cancer in women: a report from the South African National Cancer Registry

- What are the characteristics of breast cancer cases diagnosed in South African women aged 15 years and older?
- Is there an association between patient's HIV status and age, ethnicity; tumor morphology, and year of breast cancer diagnosis; as well as residential area and municipal socio-economic position?

Objectives: To describe the characteristics of breast cancer cases by HIV status in women aged 15 years and older diagnosed in South African public sector laboratories between 2004 and 2014, and to evaluate the association between patient's HIV status and patient-, disease-, and municipality-related characteristics.

Methods



“A good beginning makes a good ending." – Italian proverb

3. METHODS

The original publications presented in this thesis, along with the corresponding chapters, cover the specific methods used for each publication (please see Chapter 4: RESULTS AND ORIGINAL PUBLICATIONS). My publications have been part of collaborative initiatives with international, national, and local partners across sub-Saharan Africa. In this chapter, I provide additional aspects of overarching projects, research settings, and data availability that are not described in detail in the original publications. I will briefly outline the key projects that provided a foundation for my research, along with the partners and collaborators involved. Additionally, I will connect specific publications and aims of my thesis to these relevant projects, collaborations, and data sources.

3.1. The International epidemiology Databases to Evaluate AIDS (IeDEA)

We collaborated with the International epidemiology Databases to Evaluate AIDS (IeDEA, https://www.iedea.org/), a research consortium established in 2006 by the US National Institutes of Health. It provides a rich resource for globally diverse HIV data. The IeDEA collects and analyzes data from routine care of more than 2.2 million people living with HIV globally. In sub-Saharan Africa, IeDEA operates in 22 countries across four regions (Central, East, Southern, and West Africa) and includes 240 HIV treatment and care sites in both urban and rural areas, operating mostly at the primary or secondary care level [103]. My PhD research is nested in multiregional analyses: "Cervical Cancer Prevention and Care Cascade for Women Living with HIV in sub-Saharan Africa", approved by the IeDEA Executive Committee. This concept sheet proposed three research objectives covered in **Publications 1, 2, and 3** presented in this thesis. This thesis also outlined an implementation objective to extend the IeDEA Data Exchange Standards (IeDEA DES) by integrating variables needed to define selected indicators resulting from Publication 1. In the last trimester of my PhD trajectory, I worked closely with the IeDEA Data Harmonization Group to achieve this objective as well. However, this work will not be featured in this thesis but will only be briefly mentioned in Chapter 5.4: Implications for policy and directions for future research. The IeDEA network served as a core setting for the research presented in **Publications 1, 2, and 3**. Our collaborative efforts, however, extended beyond the

scope of the IeDEA, and encompassed partnerships with other institutions and key stakeholders in the African region through other overlapping research activities.

3.2. Advancing Cervical Cancer Screening in HIV-positive women (ACCHIVe) – The Cervical Cancer Prevention and Care Cascade

The ACCHIVe project was multiregional and multidisciplinary, done in collaboration with the four IeDEA African regions – Southern, West, East, and Central Africa – as well as with other international and national partners and stakeholders (see Figure 10).

Figure 10. *The geographic scope of the ACCHIVe Project. From "Reducing Health Inequities in the Prevention of Cervical Cancer". Swiss TPH, 2023. Reprinted with permission.*

The project had several objectives, and I was involved in Objective 1, which resulted in three original publications that are part of this thesis: **Publications 1, 2, and 3**. Therefore, in this thesis, I will elaborate further only Objective 1 and relevant aims. Objective 1 aimed to develop an evidence-based Cervical Cancer Prevention and Care Cascade framework and to implement a standardized minimum data set for the

monitoring of cervical cancer screening programs for women living with HIV in sub-Saharan Africa. Here, I briefly describe the method used in each publication, with more specific information available in the relevant sections (please see Chapter 4: RESULTS AND ORIGINAL PUBLICATIONS).

Objective 1 is furthered supplemented with the following four aims:

Aim 1: To identify and review existing international and national guidelines and policies for cervical cancer prevention and care programs in participating sub-Saharan African countries (**Publication 2**).

We systematically reviewed policies for cervical cancer prevention and care in sub-Saharan countries with an HIV prevalence ≥ 10% (in 2018), published between January 2010 and March 2022. We searched Medline via PubMed, the International Cancer Control Partnership (ICCP) website, and the national governmental websites of included countries. In addition, we consulted experts from the included countries to supplement our search. We then synthesized aspects defined in policies across different domains of the cervical cancer prevention and care continuum.

Aim 2: To identify, evaluate, and analyze the monitoring tools and data availability within existing cervical screening programs at participating IeDEA sites in sub-Saharan Africa (**Publication 3**).

I participated in conducting a facility-based, two-level cross-sectional survey based on the WHO Toolkit for cervical cancer prevention and control programs [72] and the IARC CanScren5 [108] recommendations. This survey aimed to gather and evaluate accurate, up-to-date information on the availability and delivery of cervical cancer control services, health information systems, and program monitoring. At the site level, the survey qualitatively assessed the cervical cancer prevention and care services offered at the HIV clinics participating in the IeDEA consortium across sub-Saharan Africa, as well as their monitoring efforts. At the patient level, the survey collected aggregated data from routine care provided to girls and women living with HIV at these sites.

Aim 3: To consolidate indicators for an internationally agreed-upon Cervical Cancer Prevention and Care Cascade through a Delphi consensus process and a stakeholders' meeting (**Publication 1**).

I reviewed the literature and extracted relevant indicators, grouping them into domains along the cervical cancer prevention and care continuum. From February 2021 to March 2022, we conducted a three-round, online Delphi process to reach consensus on indicators and the minimum data set needed to inform these indicators. We invited 106 experts working in sub-Saharan Africa to participate. Through an anonymous, iterative process, participants adapted the indicators to their context in Round 1, then rated them for five criteria on a 5-point Likert-type scale in Rounds 2 and 3, and finally ranked their importance in Round 3 for each domain. Consensus was reached if an indicator had a high level of agreement (more than 70% of respondents rated an indicator as 4 and 5 on Likert scale) in three or more criteria.

Within the ACCHIVe project, I also had the opportunity to lead the communication and dissemination strategy required by our funders and to translate the research findings to the non-academics and general public. This effort culminated in the development and publication of a policy brief for policymakers (please see Supplementary Chapter 10.2), a project brochure for the general public, and several social media campaigns.

3.3. The South African National Cancer Registry

To conduct the study presented in **Publication 4**, I collaborated with the South African National Cancer Registry (https://www.nicd.ac.za/centres/national-cancer-registry/). The National Cancer Registry has been conducting national pathology-based cancer registration in South Africa since 1986. Data (including demographic, clinical, and reporting source information) on cancer cases diagnosed by histology, cytology, bone marrow aspirate, or trephine are submitted to the National Cancer Registry by both private and public laboratories across South Africa. The National Cancer Registry is a division of the National Health Laboratory Services (NHLS) and aims to collect, analyze, and report on national cancer statistics to inform cancer policy and guidelines in South Africa. The NHLS is the largest diagnostic pathology service in the country, operates a network of over 260 public laboratories across nine provinces, providing laboratory and public health services to over 80% of the South African population. All data are stored electronically and sent to the NHLS' Corporate Data Warehouse (CDW) electronic data depository.

Publication 4 of this thesis was nested within **the Big Cat Study**, which was created using probabilistic record linkages of routinely collected laboratory records of people living with HIV retrieved by the NHLS, and cancer data from the South African National Cancer Registry. The methodology is described in detail by Dhokotera T et al. elsewhere [16]. In brief, the South African research team retrieved cancer records from the National Cancer Registry and HIV-related laboratory records from the NHLS CDW for the entire country for the period from 2004 to 2014. They used available identifying information (such as names, birthdays, geographic location, etc.) from corresponding patients as linkage variables. In **Publication 4** of this thesis, I evaluated breast cancer cases in the female population aged 15 years and older diagnosed in the South African public sector from 2004 to 2014. I analyzed patient-, cancer-, and municipality-related characteristics stratified by HIV status, and extracted from the cancer pathology records. For cases where HIV status was missing, the matched HIV-related laboratory record from the NHLS's CDW was used to determine the patients' HIV status. When information on ethnicity was missing, the research team at the National Cancer Registry employed a hot-deck imputation method to impute missing ethnicity, based on a reference database of surnames.

Figure 11 summarizes the data sources and variables used in the original publication. To determine socio-economic position, I collaborated with the Prof. Michael Noble from the University of Oxford, who developed and shared a ward-level South African Index of Multiple Deprivation (SAIMD) data. The SAIMD data, developed using census data, describes multiple deprivation at ward level and combines indices of four domains or dimensions of deprivation: material, employment, education, and living environment. The higher the SAIMD score, the more deprived the ward. The ward-level SAIMD was then used to determine municipal SAIMD scores by calculating the population-weighted average rank of the wards within a municipality [109-111]. Patients were assigned the municipal SAIMD score based on the location of the laboratory that reported their breast cancer diagnosis. I also used the location of the laboratory providing the breast cancer diagnosis to determine the level of urbanization, using the South African National Department of Health's data dictionary [112].

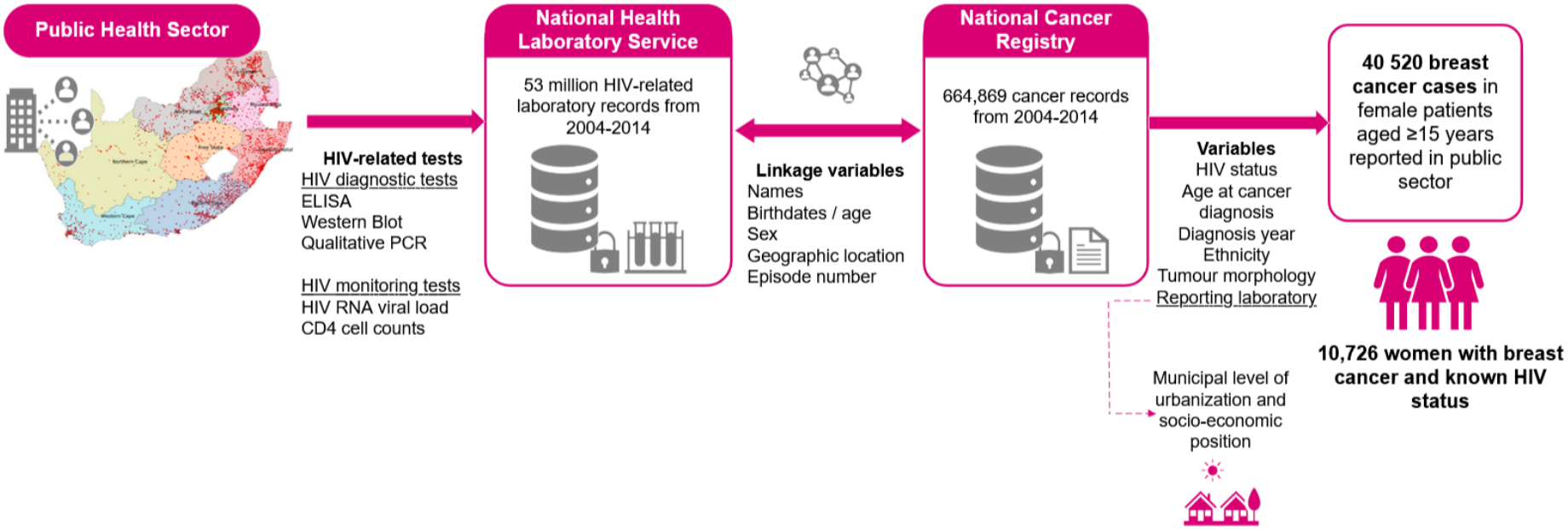
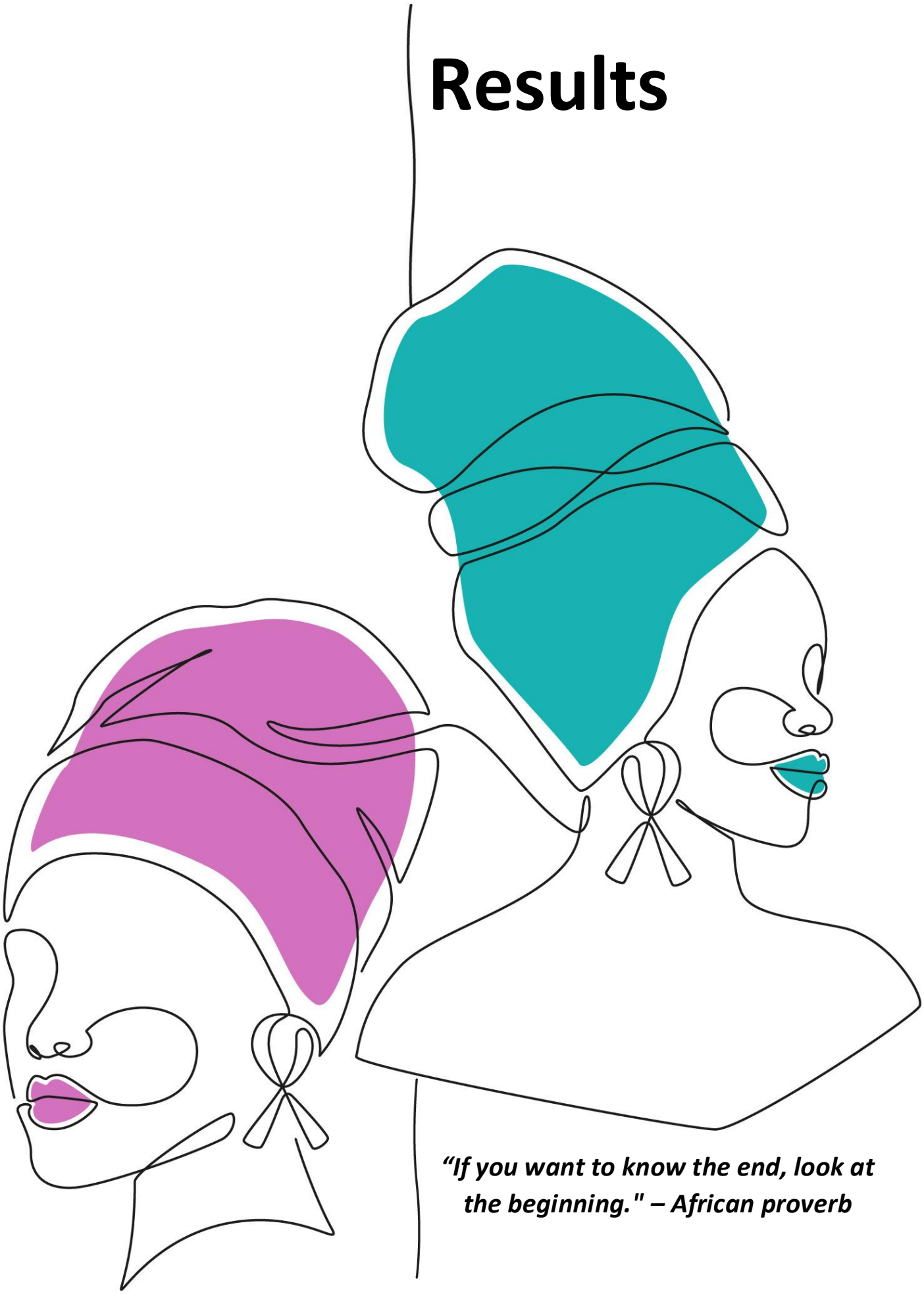


Figure 11. *The data sources and variables used in the original Publication 4 – Breast cancer in women by HIV status: a report from the South African National Cancer Registry*

Results



“If you want to know the end, look at the beginning." – African proverb

4. RESULTS AND ORIGINAL PUBLICATIONS

In this chapter, I present the four published original publications that form this thesis. This thesis is a cumulative work consisting of four publications, grouped into two sections. Each publication is introduced with a separate page that states the manuscript's title, lists the authors, and provides a brief description of my contributions.

Section I: Advancing Cervical Cancer Screening in HIV positive women (ACCHIVe) – The Cervical Cancer Prevention and Care Cascade

This section contains three publications that explore cervical cancer prevention and care continuum with a focus on women living with HIV in sub-Saharan Africa. These three publications are unique but interconnected and contribute to the development of a Cervical Cancer Prevention and Care Cascade for women living with HIV in this region. **Publication 1** presents the results of a three-round Delphi consensus process with stakeholders to develop facility-based monitoring indicators for managing and scale up cervical cancer prevention and care services in sub-Saharan Africa. **Publication 2** presents the results from reviewing national cancer policies in sub-Saharan African countries with the highest HIV prevalence. **Publication 3** presents results from a two-level, facility-based survey on the availability and use of cervical cancer prevention and care services at HIV clinics across sub-Saharan Africa.

Section II: Breast cancer in women by HIV status: a report from the South African National Cancer Registry

This section presents my research work on breast cancer in women in South Africa. It includes a nationwide study that explored differences in patient-, cancer-, and municipality-related characteristics by HIV status in patients aged 15 years and older who were diagnosed with breast cancer in the South African public health sector from 2004 to 2014. Additionally, this publication investigates the association between patients' HIV status and their age and ethnicity; tumor morphology and the year of breast cancer diagnosis; and urbanization and socio-economic position, based on municipality of the cancer-reporting laboratory.

4.1. Publication 1

Facility-based indicators to manage and scale up cervical cancer prevention and care services for women living with HIV in sub-Saharan Africa: a three-round online Delphi consensus method

Davidović Maša, Asangbeh Serra Lem, Taghavi Katayoun, Dhokotera Tafadzwa, Jaquet Antoine, Musick Beverly, van Schalkwyk Cari, Schwappach David, Rohner Eliane, Murenzi Gad, Wools-Kaloustian Kara, Anastos Kathryn, Omenge Orang'o Elkanah, Boni Simon Pierre, Duda N Stephany, von Groote Per, Bohlius Julia; International Epidemiology Databases to Evaluate AIDS.

Original article. Published in: JAIDS Journal of Acquired Immune Deficiency Syndromes. 2024 Feb 1;95(2):170-178.

Available at: https://doi.org/10.1097/QAI.0000000000003343

Own contribution: I played a key role in the conceptualization of the study, design, set up, and execution of the Delphi consensus process, which included managing recruitment and invitation procedures. I managed the data collection and analysis, and interpreted the results. Additionally, I created supplementary files shared with participants between Delphi rounds. I was instrumental in organizing and facilitating the Virtual Stakeholder Meeting 2019 and related Satellite sessions. I prepared the manuscript and crafted visuals to support findings. I wrote the first draft of the manuscript, developed visuals to support the findings, and incorporated feedback from co-authors and reviewers. I presented the preliminary results at the World Cancer Congress in Geneva, Switzerland and the final results at the Swiss Public Health Conference in Lausanne, Switzerland.

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Facility-Based Indicators to Manage and Scale Up Cervical Cancer Prevention and Care Services for Women Living With HIV in Sub-Saharan Africa: a Three-Round Online Delphi Consensus Method

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Background: Of women with cervical cancer (CC) and HIV, 85% live in sub-Saharan Africa, where 21% of all CC cases are attributable to HIV infection. We aimed to generate internationally acceptable facility-based indicators to monitor and guide scale up of CC prevention and care services offered on-site or off-site by HIV clinics.

Methods: We reviewed the literature and extracted relevant indicators, grouping them into domains along the CC control continuum. From February 2021 to March 2022, we conducted a three-round, online Delphi process to reach consensus on indicators. We invited 106 experts to participate. Through an anonymous, iterative process, participants adapted the indicators to their context

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(round 1), then rated them for 5 criteria on a 5-point Likert-type scale (rounds 2 and 3) and then ranked their importance (round 3).

Results: We reviewed 39 policies from 21 African countries and 7 from international organizations; 72 experts from 15 sub-Saharan Africa countries or international organizations participated in our Delphi process. Response rates were 34% in round 1, 40% in round 2, and 44% in round 3. Experts reached consensus for 17 indicators in the following domains: primary prevention (human papillomavirus prevention, n = 2), secondary prevention (screening, triage, treatment of precancerous lesions, n = 11), tertiary prevention (CC diagnosis and care, n = 2), and long-term impact of the program and linkage to HIV service (n = 2).

Conclusion: We recommend that HIV clinics that offer CC control services in sub-Saharan Africa implement the 17 indicators stepwise and adapt them to context to improve monitoring along the CC control cascade.

Key Words: women living with HIV, acquired immunodeficiency syndrome, early detection of cancer, cervical cancer, consensus, sub-Saharan Africa

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INTRODUCTION

Cervical cancer (CC) is the most common cancer among women living with HIV (WLHIV), who are at high risk of persistent human papillomavirus (HPV) infection and 6 times more likely to develop CC than the general population.[1,2] HIV infection contributes to 21% of all CC diagnoses among women in Africa, accounting for 85% of the global tally of women diagnosed with CC attributed to HIV.[1,3] To achieve the goal of the World Health Organization (WHO) of eliminating CC, countries in sub-Saharan Africa (SSA) must scale up access to primary, secondary, and tertiary prevention measures, especially for girls and WLHIV.[4–6] To improve CC control programs, clinicians, researchers, and policymakers need high-quality routine health facility data,[7,8] which can be collected by monitoring each step of the path that people take through the health system. To create a monitoring plan for cancer control, each sequential step through a complex health system must be quantified within the framework of a cascade[9] and indicators must be specified for each step.[10,11] Cascades are widely used conceptual models that support monitoring, assess engagement, and identify gaps in services.[9,12,13] Several studies have taken this approach to evaluating the performance of CC control programs for WLHIV in SSA,[14–20] but they did not use standardized indicators, so it is difficult to compare their findings.[14–20] Indicators that consider HIV status are often omitted from cancer control policies, even in countries with high HIV burden,[21] where they are most necessary.[22] Most cancer control polices in these countries advice leveraging existing infrastructure and integrating CC prevention and care services into existing HIV programs to facilitate access to and scale up of these services and eventually significantly reduce CC incidence and mortality.[23–27] But today, data on access to and uptake of services for women attending HIV clinics in SSA are limited or rare, although electronic data systems are widely available.[21,22,28]

We urgently need standardized indicators for each step in the CC prevention and care cascade to measure and compare access with the quality of the services offered to girls and WLHIV, so we used a Delphi process to bring experts to consent on facility-based indicators for monitoring, managing, and scaling up the CC prevention and care cascade through which girls and women attending HIV clinics in SSA progress.

METHODS

Study Settings

We collaborated with the International epidemiology Databases to Evaluate AIDS consortium (IeDEA, https://www.iedea.org/), a network that collects and analyzes data from routine care of more than 2.2 million people living with HIV globally. In SSA, IeDEA is present in 22 countries across 4 regions (Central, East, Southern, and West Africa) and comprises 240 HIV treatment and care sites in both urban and rural areas, operating mostly at the primary or secondary care level.[29] The study received an ethics waiver from the Cantonal Ethics Committee of Bern (BASEC-Nr: Req-2020-00748).

Literature Review

Three researchers (M.D., K.T., and S.L.A.) reviewed the literature to identify relevant indicators for monitoring CC control programs. We first reviewed the recent WHO toolkit, *Improving Data for Decision Making in Global Cervical Cancer Programmes* (IDCCP), which describes indicators and best monitoring practices,[30] and the International Cancer Control Partnership database.[31] Next, we included the most recent national cancer control policies, strategic plans, and where available, national plans for controlling noncommunicable diseases in SSA countries. We explored national health ministry websites and online web tools and contacted experts in the field to identify the relevant unpublished literature. We included documents published between 2010 and 2020 in English and French. Two researchers (M.D. and S.L.A.) independently extracted relevant indicators and the definitions of numerators and denominators when they were available. These researchers compared the results, deduplicated, and grouped similar indicators. When they disagreed, they consulted a third investigator (K.T.) to arrive at consensus. From our list of extracted indicators, we deliberately preselected those that could be quantified with data collected at HIV clinics during routine care. We did not limit the number of indicators, but we excluded indicators that would require facilities to conduct surveys or patients to fill out satisfaction questionnaires, for example, qualitative indicators that measure CC awareness or quality of care, patient experience, and satisfaction.

The Expert Panel

Based on predefined selection criteria (see File S1, Supplemental Digital Content, http://links.lww.com/QAI/C163), we recruited experts in CC or HIV/AIDS prevention and care in SSA through the IeDEA network. We also invited participants of the 2019 workshop "CC Prevention and Care Cascade in WLHIV in SSA," hosted by the third IeDEA All Africa meeting. Expert Panel (EP) members were asked to

volunteer their participation in the Delphi process and to attend our online meetings. We aimed for equal geographic and sex distribution of EP members.

Delphi Process

We conducted a three-round online Delphi process (see Figure S1, Supplemental Digital Content, http://links.lww.com/QAI/C162), after recommendations from guidelines and reviews.[32–36] The Delphi process is a structured method for gathering and distilling the collective knowledge and opinions of a group of topic experts. We developed and piloted a Delphi questionnaire in English and French, which included (1) informed consent, (2) study description and instructions, and (3) general and demographic questions. The questionnaire also included (4) the indicators we had identified, preselected, and then adapted or revised with the EP members during the process, along with any remaining open questions. Rating and ranking instructions (5) were also provided. We emailed EP members and asked them to use the Qualtrics^{XM} survey platform to participate anonymously in the online Delphi process.

The first Delphi round questionnaire included a preliminary list of the 30 preselected indicators in tabular format,[37] listing title and definition, purpose and rationale, measurement method, data collection methodology and frequency, data disaggregation, guidelines for interpreting and using data, and relevant additional information. The questionnaire included multiple choice questions about additional items for indicators, for example, definition of the population, appropriate levels of disaggregation, age ranges, and time periods. We used the responses to modify indicators in subsequent rounds, based on majority rule. Then, we grouped the indicators into the 6 domains that match the steps of the CC control continuum (Fig. 1). In the second Delphi round, we presented these revised indicators to our experts, along with summaries of the first-round comments. We asked EP members whether they agreed with the updates or believed they needed further discussion. We also told them that, once they reached consensus on indicators (high or very high rating by at least 70% of respondents, see below for details), we would implement the variables needed to calculate those indicators into the IeDEA Data Exchange Standard. Experts were told to rate the revised indicators on a 5-point Likert-type scale (1-very low and 5-very high) for 5 rating criteria: relevance, feasibility, comparability, reliability, and understandability (see File S2, Table S3, Supplemental Digital Content, http://links.lww.com/QAI/C164). We drew our selection of the type of Likert scale, and our definitions and the number of rating criteria from the literature and made final decisions within our team through the voting process. Between the second and third Delphi rounds, we organized 4 satellite sessions and an online stakeholder meeting. At the satellite sessions, we discussed definitions of indicators and data elements, key populations, age ranges, time periods, rating results, comments we had selected from previous rounds, and domains. The EP members shared and discussed their concerns and ideas and proposed solutions. At the final stakeholder meeting, we presented and discussed successful regional models of CC management and data collection and future activities. Professional moderators guided all sessions, and we used interpreters to ensure that language was not a barrier to joining the discussions. In the third Delphi round, we shared a summary of comments from previous rounds and minutes of our meetings (see File S3, Supplemental Digital Content, http://links.lww.com/QAI/C165). We asked the EP to rerate indicators based on our 5 rating criteria. We presented again 30 indicators, although some did not reached consensus in the second round because we discussed and adjusted indicators based on feedback we received during satellite sessions. The EP then ranked the importance of each indicator, stratified by the 6 domains. Throughout the process, participants could comment in open-ended question

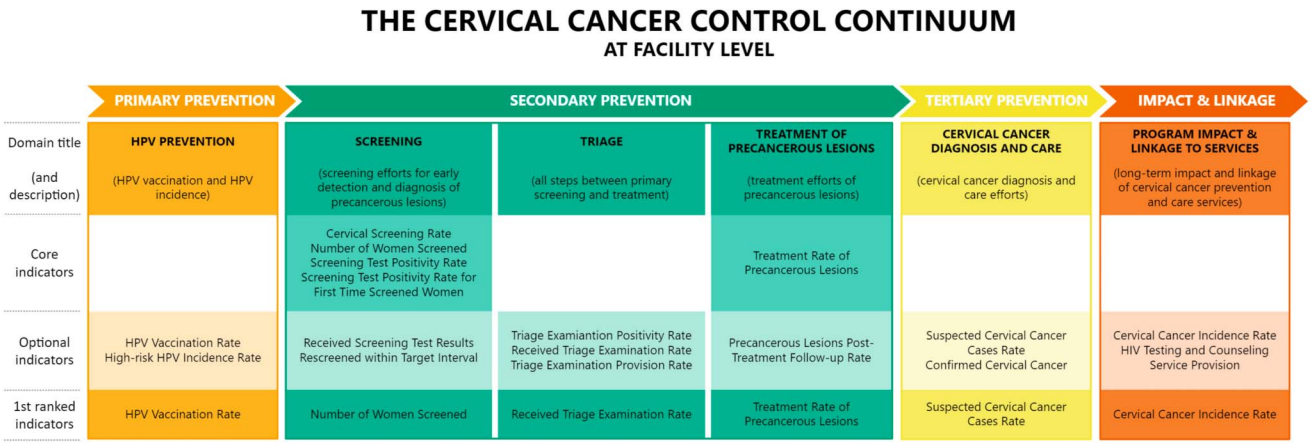

FIGURE 1. The Cervical Cancer Control Continuum at facility level: the overview of domains, core, optional, and first ranked indicators per each domain that reached consensus in round 3. Consensus is reached if the indicator had a high level of agreement (more than 70% of respondents rated an indicator as 4 and 5 points on Likert scale) in 3 or more criteria. Within each domain, the core and optional indicators are ordered based on their rating results, with the highest-rated indicator placed at the top. Core indicators are indicators that reached a high level of agreement in all 5 criteria, and optional indicators are those with a high level of agreement in 3 or 4 criteria. The indicator ranked as the most important in each domain is presented as the first ranked indicator.

fields. Two researchers (M.D. and A.Z.) could access the database containing the responses; feedback could not be linked back to individuals. In each Delphi round, we sent weekly reminders to participants who had not yet submitted their answers.

Data Analysis

We used descriptive statistics to report characteristics of EP members and participation, response, and completion rates; these equations are detailed in Table S1, Supplemental Digital Content, http://links.lww.com/QAI/C162. Rating and ranking results are presented by level of agreement and consensus, ranking score (RS), and total rank; descriptions of rating and ranking calculations are provided in File S4, Supplemental Digital Content, http://links.lww.com/QAI/C166. We defined consensus as the median score above our predefined threshold and a high level of agreement (see File S2, Supplemental Digital Content, http://links.lww.com/QAI/C164, Definition of consensus),[38,39] defined as an indicator rated 4 (high) or 5 (very high) points on the Likert scale for at least 3 of 5 criteria (relevance, feasibility, comparability, reliability, and understandability) by 70% of respondents. We provided an illustrated overview and comprehensive tables for indicators that reached consensus in round 3, basing our presentation on international recommendations. Tables include title, definition, calculation, purpose and rationale, data source, frequency, disaggregation, and guidelines. We used thematic analysis to interpret qualitative data from open-ended questions (see File S5, Supplemental Digital Content, http://links.lww.com/QAI/C167).[40,41]

RESULTS

Literature Review

We identified and reviewed 46 documents (39 in English and 7 in French): 39 policies from 21 African countries and 7 from international organizations and 2 web tools for cancer-related data analysis (https://canscreen5.iarc.fr/ and https://nordscreen.org/) (see Table S2, Supplemental Digital Content, http://links.lww.com/QAI/C162). In total, we extracted and reviewed 509 indicators; of these, 52 were extracted from the WHO IDCCP Toolkit.[30] Two researchers deduplicated and then grouped the extracted indicators based on similarity. We then proposed 30 indicators to the EP.

Characteristics of Expert Panel Members

We emailed 106 experts (85 in Round 1, 84 in Round 2, and 101 in Round 3) and invited them to participate. In the second round, 1 participant opted out. In the third round, we invited additional experts who had expressed interest in joining the stakeholder meeting. In total, 72 individuals participated in at least 1 round (46 in Round 1, 40 in Round 2, and 55 in Round 3). Fifteen African countries were represented in the EP (Fig. 2), and it was gender-balanced (52% women). Most members were researchers (56%) and clinicians (31%). 68% were affiliated with the IeDEA consortium, and about half (48%) worked in Southern Africa (see Table S3, Supplemental Digital Content, http://links.lww.com/QAI/C162). Most participants self-reported that they had either less than 5 years (31%) of experience or 10–20 years (34%) of experience in CC prevention and care and 10–20 years (39%) in HIV/AIDS care and treatment. A third of participants reported additional experience in other areas of research or health care (see Table S4, Supplemental Digital Content, http://links.lww.com/QAI/C162).

Delphi Rounds

The response rate (number of participants who completed the survey/number of emailed participants) was 34% in round 1, 40% in round 2%, and 44% in round 3 (see Table S3, Supplemental Digital Content, http://links.lww.com/QAI/C162 for completion rates and participation rates). The definitions of key population were guided by WHO recommendations on CC screening and treatment for WLHIV,[42] informed by participants' answers in the first and second round, and discussed and agreed on during satellite sessions: "Women living with HIV/AIDS who are enrolled in care and had at least 1 HIV clinic visit during the period of interest" and who aged "25–49 years" and "Girls living with HIV enrolled in care with at least 1 HIV clinic visit during the period of interest" and who aged "9–14 years". Where applicable, we incorporated these definitions for all indicators in the final rating and ranking session.

In the second and third round, EP members rated the 30 proposed indicators, and consensus (at least 70% agreement in 3 or more criteria) was reached on 13 indicators in round 2 (see Figure S2, Supplemental Digital Content, http://links.lww.com/QAI/C162) and 17 indicators in round 3 (Fig. 3). The 17 indicators that reached consensus in round 3 covered all domains of the CC prevention and care continuum: primary prevention (HPV prevention, n = 2), secondary prevention (screening, n = 8; triage, n = 6; treatment of precancerous lesions, n = 4), tertiary prevention (CC diagnosis and care, n = 5), and long-term impact of the program and linkage to HIV services (n = 5). These are comprehensively described in File S6, Supplemental Digital Content, http://links.lww.com/QAI/C168. In the *primary prevention (HPV prevention)* domain, both of the proposed indicators reached consensus. In the *secondary prevention* domain, 6 of 8 screening indicators reached consensus; half of *triage* indicators (3/6) and *treatment of precancerous lesions* indicators (2/4) reached consensus. In the *tertiary prevention (CC diagnosis and care)* domain and the *long-term program impact and linkage to HIV services* domain, 2 of 5 proposed indicators reached consensus.

Five indicators obtained a high level of agreement (>70% of participants) in all 5 criteria, and we labeled these as core indicators. We labeled the other 12 indicators as optional. Of the 5 core indicators, 4 belonged to the *secondary prevention (screening)* domain: Cervical Screening Rate, Number of Women Screened for Cervical Precancer, Screening Test Positivity Rate, and Screening Test Positivity Rate for First Time Screened Women. One belonged to the *secondary prevention (treatment of precancerous lesions)*

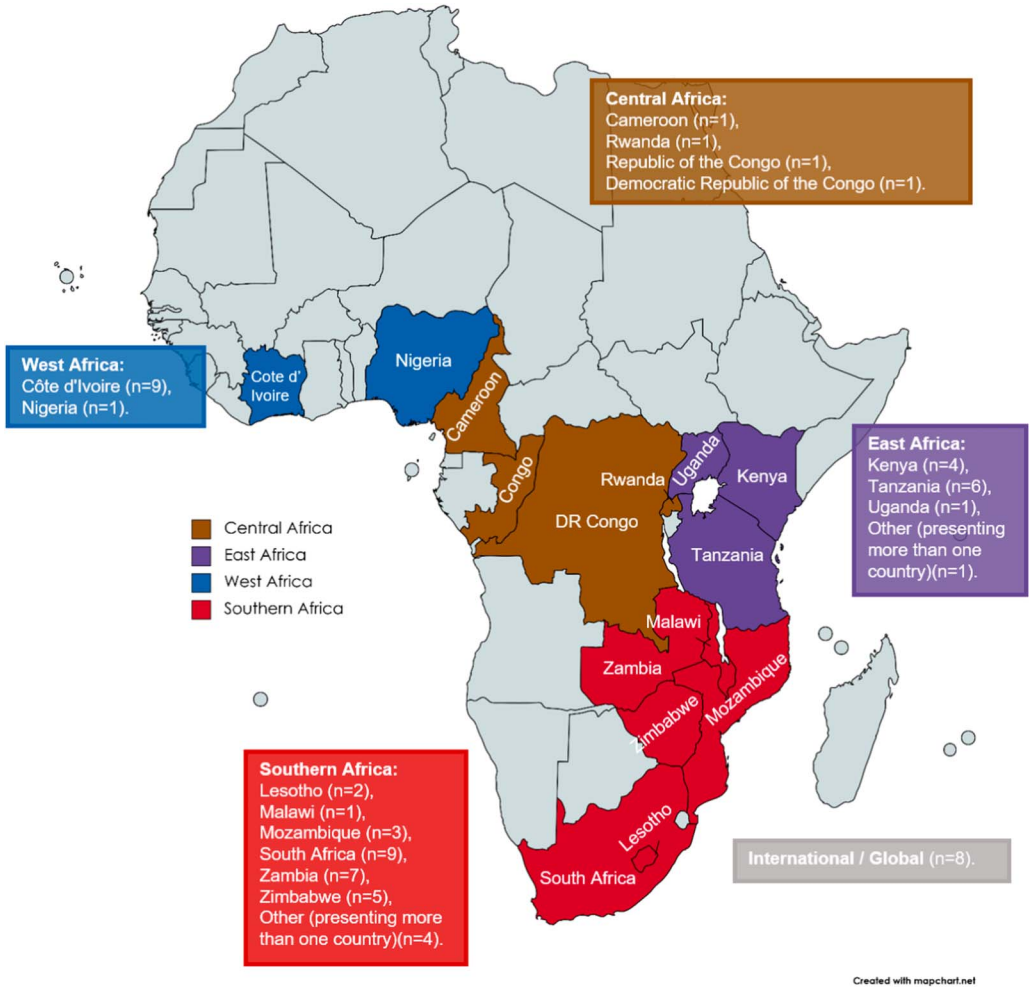

FIGURE 2. Representative countries in the EP in all 3 Delphi rounds (total participants, n = 65).

domain: Treatment Rate of Precancerous Lesions (Fig. 3). The same indicators, except Screening Test Positivity Rate for First Time Screened Women, reached consensus for all 5 criteria in round 2. Cervical Cancer Incidence Rate reached consensus for all 5 criteria in round 2, but not round 3. More than 70% of EP members rated the relevance of 16 indicators in round 2 and 17 indicators in round 3 as 4 (high) or 5 (very high). In round 3, all indicators that reached consensus had been rated 4 or 5 for comparability and understandability. In round 2, only 13 indicators were rated 4 or 5 for comparability, and 14 indicators were rated 4 or 5 for understandability (Fig. 3). Ratings on feasibility and reliability were lower; only 6 indicators in rounds 2 and 3 were rated 4 or 5 for feasibility and reliability. Between rounds 2 and 3, the greatest change in the level of agreement was for Triage Examination Positivity Rate: Feasibility increased by 27% (from 35% to 62%) and understandability by 29% (from 62% to 91%). Of the 13 indicators that failed to reach consensus in round 3, 10 were rated 4 or 5 for relevance by more than 70% of participants; none was rated 4 or 5 for feasibility, comparability, or reliability (see Figure S2, Supplemental Digital Content, http://links.lww.com/QAI/C162).

Our analysis of the qualitative data we collected in all 3 rounds revealed that the topic of most concern was improving the definitions of indicators (eg, age ranges). Several participants believed that it could be difficult to collect the data that informed the indicators during routine care and to disaggregate that information, especially in resource-limited settings and settings where cervical screening services are offered off-site. We integrated these concerns in round 2, when we drafted the agenda for the satellite meetings. For example, at the satellite sessions, we discussed the recent update to WHO screening and treatment guidelines for CC, in which WHO newly recommended that WLHIV should take an HPV DNA primary test and then a triage test if they were found to be HPV positive.[42] Members presented their ideas and suggestions for overcoming challenges to implementing these guidelines, for example, the feasibility of collecting the data (see File S3, Supplemental Digital Content, http://links.lww.com/QAI/C165).

Table 1 and Figure 1 present the 17 indicators that reached consensus in round 3, ranked by importance and stratified by domain. The highest ranked indicators in each domain were HPV Vaccination Rate in *primary prevention*,

		Rating criteria										No. of Criteria‡	
		Relevance		Feasibility		Comparability		Reliability		Understandability			
Domain†	CORE INDICATORS	R2	R3	R2	R3	R2	R3	R2	R3	R2	R3	R2	R3
2	Cervical Screening Rate	97%	100%	74%	96%	85%	89%	74%	82%	94%	96%	5	5
2	Number of Women Screened for Cervical Pre-cancer	94%	91%	79%	96%	76%	82%	79%	82%	94%	96%	5	5
2	Screening Test Positivity Rate	97%	98%	82%	84%	94%	76%	85%	80%	94%	89%	5	5
4	Treatment Rate of Precancerous Lesions	97%	98%	76%	80%	88%	87%	82%	82%	94%	91%	5	5
2	Screening Test Positivity Rate for First Time Screened	88%	93%	68%	71%	85%	80%	68%	71%	91%	96%	3	5
Domain†	OPTIONAL INDICATORS	R2	R3	R2	R3	R2	R3	R2	R3	R2	R3	R2	R3
5	Suspected Cervical Cancer Cases Rate	88%	93%	71%	80%	71%	73%	62%	64%	88%	98%	4	4
3	Triage Examination Positivity Rate	79%	89%	35%	62%	59%	73%	53%	76%	62%	91%	1	4
6	Cervical Cancer Incidence Rate	94%	91%	82%	56%	97%	87%	79%	58%	97%	91%	5	3
1	High Risk HPV Incidence Rate	88%	84%	59%	53%	76%	71%	74%	69%	91%	84%	4	3
5	Confirmed Cervical Cancers	85%	96%	56%	56%	76%	84%	53%	69%	82%	96%	3	3
1	HPV Vaccination Rate	97%	89%	65%	62%	76%	82%	62%	60%	94%	96%	3	3
4	Precancerous Lesions Post-Treatment Follow-Up Rate	97%	91%	53%	58%	74%	80%	56%	69%	97%	91%	3	3
2	Received Screening Test Results	82%	89%	59%	51%	82%	73%	65%	47%	82%	84%	3	3
2	Rescreened within Recommended Screening Interval	82%	93%	56%	44%	76%	71%	62%	58%	82%	91%	3	3
6	HIV Testing and Counseling Service Provision Rate	74%	84%	56%	60%	68%	71%	62%	67%	74%	84%	2	3
3	Received Triage Examination Rate	74%	86%	53%	55%	68%	70%	56%	66%	62%	84%	1	3
3	Triage Examination Provision Rate	65%	76%	35%	51%	56%	71%	44%	60%	62%	80%	0	3
	Total number of indicators that reached 70% agreement	16	17	6	6	13	17	6	6	14	17		

† Domains: 1) Primary prevention – HPV prevention, 2) Secondary prevention – Screening, 3) Secondary prevention – Triage, 4) Secondary prevention – Treatment of precancerous lesions, 5) Tertiary Prevention – Cervical cancer diagnosis and care, 6) Long-term program impact and linkage to HIV services; ‡ No. of criteria – the number of criteria with high level of agreement (> 70% participants rated as 4 (High) or 5 (Very high) points on the Likert scale). Indicators are ordered by highest to lowest number in R3, followed by the highest to lowest number in R2; Abbreviations: R2 – Round 2; R3 – Round 3

FIGURE 3. List of indicators that reached consensus in round 3. Consensus was reached if more than 70% of participants rated the indicator as 4 (high) or 5 (very high) points on the Likert scale in 3 or more criteria.

Number of Women Screened for Cervical Precancer in *secondary prevention (screening)*, Received Triage Examination Rate in *secondary prevention (triage)*, Treatment Rate of Precancerous Lesions in *secondary prevention (treatment of precancerous lesions)*, Suspected Cervical Cancer Cases Rate in *tertiary prevention (CC diagnosis and care)*, and Cervical Cancer Incidence Rate in *long-term program impact and linkage to HIV service*.

DISCUSSION

We worked with international experts to come to consensus on facility-based indicators for managing and scaling up CC prevention and care services offered to girls and WLHIV, who receive care at HIV clinics across SSA. The group reached consensus (at least 70% agreement in 3 or more criteria) on 17 indicators in the domains of primary prevention (HPV prevention, n = 2), secondary prevention (screening, triage, treatment of precancerous lesions, n = 11), tertiary prevention (CC diagnosis and care, n = 2), and long-term impact of the program and its linkage to HIV services (n = 2). Five indicators from the *secondary prevention (screening and treatment of precancerous lesions)* domain garnered at least 70% agreement for all criteria (relevance, feasibility, comparability, reliability, and understandability) the experts used to rate them.

We took a comprehensive methodological approach that comprised a rigorous EP selection process and iterative online Delphi rounds in which discussions were guided and participants presented structured feedback. Questionnaires contained detailed instructions in 2 languages. We assembled an EP of participants from a variety of professional backgrounds and levels of experience; to increase the likelihood, our results would be generalizable and applicable across contexts. We were limited by several factors, including low response rates (34%–45%) in all rounds. In our study, a long questionnaire may have reduced our response rate, especially in round 1; the first round questionnaire was the longest and most complex, containing items to help participants adapt the indicators. Finally, owing to the COVID-19 pandemic, we replaced our planned face-to-face events with online discussions, which may have reduced the EP members' motivation to participate.

Some reviews found that three-round Delphi processes reported response rates between 45% and 93%,[43] but less than a third (31%) of included studies had reported response rates for all rounds.[39] Differences in reported response rates can be also explained by different denominators used to calculate them (eg, number of emailed participants, participants who agreed to participate, or participants who completed the survey in the previous round). To improve the response rates in our study, we used online management survey software to design and administrate user-friendly survey to maintain

TABLE 1. Ranking of Indicators That Reached Consensus per Domains in Round 3 by Importance

Rank* (Score)	Indicator's Title and Definition
Domain: Primary Prevention—HPV Prevention	
1 (85)	HPV Vaccination Rate
	HPV vaccinated "girls living with HIV enrolled in care with at least 1 HIV clinic visit during the period of interest" aged 9–14 yrs
2 (50)	High-Risk HPV Incidence Rate
	Newly diagnosed high-risk HPV cases among "girls and women living with HIV/AIDS enrolled in care with at least 1 HIV clinic visit during the period of interest" in a specific age range in a 12-month period
Domain: Secondary Prevention—Screening	
1 (312)	Number of Women Screened for Cervical Precancer†
	Number of screened "women living with HIV/AIDS aged 25–49 years enrolled in care with at least 1 HIV clinic visit during the period of interest"
2 (304)	Cervical Screening Rate‡
	Screened "women living with HIV/AIDS aged 25–49 years enrolled in care with at least 1 HIV clinic visit during the period of interest"
3 (237)	Screening Test Positivity Rate for the Primary Screening Test
	Screened "women living with HIV/AIDS aged 25–49 years enrolled in care with at least 1 HIV clinic visit during the period of interest" who received a positive primary screening test result in a 6-month period
4 (156)	Received Screening Test Results
	"Women living with HIV/AIDS aged 25–49 years enrolled in care with at least 1 HIV clinic visit during the period of interest" who received their screening test results in a 6-month period
5 (113)	Screening Test Positivity Rate for the Primary Screening Test for First Time Screened Women
	The first time screened "women living with HIV/AIDS aged 25–49 years enrolled in care with at least 1 HIV clinic visit during the period of interest" who received a positive primary screening test result in a 12-month period
6 (75)	Rescreened after a previous Negative Result, within Recommended Screening Interval
	"Women living with HIV/AIDS aged 25–49 years enrolled in care with at least 1 HIV clinic visit during the period of interest" who were rescreened (after a previous negative result) within the recommended screening interval
Domain: Secondary Prevention—Triage	
1 (215)	Received Triage Examination Rate
	Screen-positive "women living with HIV/AIDS aged 25–49 years enrolled in care with at least 1 HIV clinic visit during the period of interest" who received a triage examination in a 12-month period
2 (185)	Triage Examination Positivity Rate
	Screen-positive "women living with HIV/AIDS aged 25–49 years enrolled in care with at least 1 HIV clinic visit during the period of interest" with a positive triage examination result in a 12-month period
3 (116)	Triage Examination Provision Rate
	Screen-positive "women living with HIV/AIDS aged 25–49 years enrolled in care with at least 1 HIV clinic visit during the period of interest" who attended the triage visit and received a triage examination in a 12-month period
Domain: Secondary Prevention—Treatment of precancerous lesions	
1 (176)	Treatment Rate of Precancerous Lesions
	Screen-positive "women living with HIV/AIDS aged 25–49 years enrolled in care with at least 1 HIV clinic visit during the period of interest" who have received treatment in a 6-month period
2 (111)	Precancerous Lesions Post-Treatment Follow-Up Rate
	"Women living with HIV/AIDS aged 25–49 years enrolled in care with at least 1 HIV clinic visit during the period of interest" treated for precancerous lesions who return for a post-treatment follow-up screening test in a 12-month period
Domain: Tertiary Prevention—CC diagnosis and care	
1 (197)	Suspected Cervical Cancer Cases Rate
	Screened "women living with HIV/AIDS aged 25–49 years enrolled in care with at least 1 HIV clinic visit during the period of interest" with suspected cervical cancer in a 12-month period
2 (86)	Confirmed Cervical Cancers Rate
	Screen-positive "women living with HIV/AIDS aged 25–49 years enrolled in care with at least 1 HIV clinic visit during the period of interest" diagnosed with invasive cervical cancer in a 12-month period
Domain: Long-term program Impact and Linkage of HIV Services	
1 (200)	Age-Specific Cervical Cancer Incidence Rate
	New invasive cervical cancer cases diagnosed in "women living with HIV/AIDS enrolled in care with at least 1 HIV clinic visit during the period of interest" in a specific age group or range in a 12-month period
2 (112)	HIV Testing and Counseling Service Provision Rate
	Women with previously unknown HIV status who received testing and counseling service for HIV at their cervical screening visit, and now know their HIV status in a 12-month period

*Rank position and RS per each domain. To determine the RS, we first calculated frequency (how many respondents placed an indicator as first, second, third etc., within each domain). We multiplied frequency by the weight of the ranked position: First place was the highest and last place was the lowest: RS = 1W1 + x2W2 + x3W3 + x4W4… where x is the frequency (response count) for the indicator choice and W is the weight of the ranked position. Then we ordered RS from the highest to lowest and assigned the ranks: 1 for the first highest RS within domain, 2 for the second highest RS etc.; File S4, Supplemental Digital Content, http://links.lww.com/QAI/C166, Quantitative analysis (rating and ranking) provides step-by-step instructions how ranking was performed.

†This is an absolute number.

‡This is a proportion.

participants' motivation and to send weekly reminders to nonrespondents.[35]

The WHO IDCCP Toolkit[30] and previously published studies that evaluated CC control services for WLHIV in SSA focused primarily on the secondary prevention portion of the cascade (screening, treatment of precancerous lesions, and follow-up). Our study identified core and optional indicators across the CC control continuum, from primary prevention to long-term impact and linkage of services. In general, core indicators result in better data and better use of data to improve programs.[13,30] Optional indicators add insight into program performance and outcome and capture aspects of patient care in more detail.[30] We discussed some of our optional indicators at the satellite meetings, especially those related to updated CC screening and treatment recommendations of WHO. These discussions highlighted the importance of triage test in screening WLHIV, which may be why 2 indicators from the domain *triage* reached consensus in round 3 instead of round 2. But both these indicators were still rated low on feasibility and reliability, perhaps because most cervical screening programs in SSA still rely on visual inspection with acetic acid–based "screen and treat" strategies and have not yet implemented HPV testing, followed by a triage test.[22] Although EP members agreed that all optional indicators were highly relevant, comparable, and understandable (high level of agreement in these criteria) at satellite meetings, they expressed their concern that it was not feasible to collect the necessary data; this concern was reflected in their ratings. EP members also recognized that it would be useful to disaggregate indicators to identify existing differences in service access and quality within subpopulations[13] but were concerned that it would make data collection, management, and aggregation more complex.

In resource-limited settings, we recommend prioritizing the core indicators that garnered the highest level of agreement for feasibility and reliability. Facilities with mature programs, robust data systems, available resources, or needs to monitor specific priorities may consider to include optional indicators. Nevertheless, to perform a comprehensive cascade analysis, it is needed to consider all domains of CC control and include both core and optional indicators. In future, researchers and program managers should weigh the benefits of collecting data to inform these indicators against their capacity to collect high-quality data and manage it. Our next step will be to define a minimum data set and variables needed to inform the core and optional indicators to facilitate data collection at HIV facilities offering CC control services. We will implement the variables within the IeDEA Data Exchange Standard, so we can analyze, interpret, and disseminate CC data and support efforts[44] to track the progress of the WHO CC Elimination Strategy,[4] with a focus on girls and WLHIV. International research collaborations, for example, IeDEA, could increase local capacity to collect and analyze patient-level facility-based data through partnered research activities and help facilities and programs overcome infrastructure or capacity limitations.[26] These activities require dedicated resources because each step of the CC prevention and care cascade requires comprehensive assessment. Because many countries in SSA are investing in cost-effective efforts to improve access to and to manage CC screening and treatment services for WLHIV, we have reason to believe that assessing some indicators might soon become more feasible.[45] We should support these efforts by improving monitoring along with data collection and management.

CONCLUSIONS

We recommend implementing the 17 indicators (see File S6, Supplemental Digital Content, http://links.lww.com/QAI/C168) we identified into routine data collection at HIV clinics and facilities in SSA that offer CC prevention and care services, and this has the potential to significantly increase the quality of data collection and reporting. Programs and facilities can use these core and optional indicators to improve monitoring and evaluation in a variety of contexts, so they can improve CC control services for WLHIV.

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4.2. Publication 2

Cervical cancer prevention in countries with the highest HIV prevalence: a review of policies

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Own contribution: I was actively involved in the study's conceptualization and collaborated closely with the first author in identifying relevant publications, reviewing selected policies, and managing the data extraction and cleaning processes. I also contributed to the data analysis and interpretation. Additionally, I provided a critical reviews and revisions for the initial and subsequent drafts of the manuscripts, as well as the supplementary material.

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RESEARCH

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Cervical cancer prevention in countries with the highest HIV prevalence: a review of policies

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Abstract

Introduction: Cervical cancer (CC) is the leading cause of cancer-related death among women in sub-Saharan Africa. It occurs most frequently in women living with HIV (WLHIV) and is classified as an AIDS-defining illness. Recent World Health Organisation (WHO) recommendations provide guidance for CC prevention policies, with specifications for WLHIV. We systematically reviewed policies for CC prevention and control in sub-Saharan countries with the highest HIV prevalence.

Methods: We included countries with an HIV prevalence ≥ 10% in 2018 and policies published between January 1st 2010 and March 31st 2022. We searched Medline via PubMed, the international cancer control partnership website and national governmental websites of included countries for relevant policy documents. The online document search was supplemented with expert consultation for each included country. We synthesised aspects defined in policies for HPV vaccination, sex education, condom use, tobacco control, male circumcision,cervical screening, diagnosis and treatment of cervical pre-cancerous lesions and cancer, monitoring mechanisms and cost of services to women while highlighting specificities for WLHIV.

Results: We reviewed 33 policy documents from nine countries. All included countries had policies on CC prevention and control either as a standalone policy (77.8%), or as part of a cancer or non-communicable diseases policy (22.2%) or both (66.7%). Aspects of HPV vaccination were reported in 7 (77.8%) of the 9 countries. All countries (100%) planned to develop or review Information, Education and Communication (IEC) materials for CC prevention including condom use and tobacco control. Age at screening commencement and screening intervals for WLHIV varied across countries. The most common recommended screening and treatment methods were visual inspection with acetic acid (VIA) (88.9%), Pap smear (77.8%); cryotherapy (100%) and loop electrosurgical procedure (LEEP) (88.9%) respectively. Global indicators disaggregated by HIV status for monitoring CC programs were rarely reported. CC prevention and care policies included service costs at various stages in three countries (33.3%).

Conclusion: Considerable progress has been made in policy development for CC prevention and control in sub Saharan Africa. However, in countries with a high HIV burden, there is need to tailor these policies to respond to the

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specific needs of WLHIV. Countries may consider updating policies using the recent WHO guidelines for CC prevention, while adapting them to context realities.

Keywords: Cervical cancer, WLHIV, National policies, Prevention and control, Sub Saharan Africa

Introduction

Women living with HIV (WLHIV) are at higher risk of developing cervical cancer (CC) compared with HIV negative women [1]. Women with HIV are at higher risk for persistent Human Papillomavirus (HPV) infection, lower chances of clearing infection, faster progression from infection to CC, lower regression of cervical precancerous lesions, and higher recurrence following treatment, compared with HIV negative women [2]. This double HIV-CC burden exacerbates the disparities in CC between High Income Countries (HICs) and Low and Middle Income Countries (LMICs) [3]. In sub-Saharan Africa (SSA), morbidity and mortality rates from both HIV and CC are among the highest globally [1]. In 2018, 38 of the 50 countries with the highest-ranking Population Attributable Fractions (PAF) for CC and HIV were in the African region. The PAF in SSA was 21·0% (15·6–26·8) compared to less than 2% in all other regions globally. The top nine countries with the highest PAFs were in Southern Africa ((PAF: 53·2% (49·1–56·8)) and are included in this review [1, 4]. Effective prevention programmes in HICs have significantly reduced the incidence of CC. However, CC screening in LMICs remains undermined by competing health priorities, resource challenges and lack of monitoring of existing programmes [5, 6].

In November 2020, the World Health Organization (WHO) launched the global strategy for the elimination of CC as a public health problem, defining the 90–70-90 targets [7]. To eliminate CC within a century, 90% of girls should be vaccinated by age 15, 70% of women should be screened with a high precision test by 35 and 45 years of age, and 90% of women with precancerous lesions and invasive CCshould receive treatment and care at national level by 2030. In 2021, the WHO updated guidelines for screening and treatment of cervical precancerous lesions highlighting specific recommendations for WLHIV, including age of first screening for WLHIV [8]. Importantly, the WHO highlights the need for quality control of screening services nationally and globally, including the collection of data to measure standardised process, performance, and impact indicators.

National policies to eliminate CC provide the foundation for the implementation and sustainability of CC screening programmes and demonstrate governments' commitment to CC prevention and control. In countries with a high HIV burden, this is especially important. Data on country-specific recommendations for CC prevention for WLHIV is rare. We reviewed policies and recommendations for CC prevention and control in SSA countries with the highest HIV prevalence with special focus on the indicators and standards used to monitor the programmes.

Methods

We conducted a systematic review of national policies, plans, guidelines and strategies for CC prevention and control (simply referred to here as "policies") in SSA countries with the highest HIV prevalence according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9].

Eligibility criteria for countries and documents

We included countries with an HIV prevalence of 10% and above in 2018 [10]. The prevalence threshold was an arbitrary cut-off for the study. For eligible countries, we identified relevant documents, including national policies, plans, strategies and guidelines for non-communicable diseases (NCDs), cancer, and CC prevention and control without language restrictions published between January 2010 and May 2019. We updated our search in April 2022 to include all policy documents published and unpublished after May 2019 until March 2022. The choice of January 2010 was informed by the oldest policy document in use at the time of the study in Lesotho, which was dated 2011. Documents that did not contain any information on CC prevention were excluded.

Information sources and searches

We identified documents through a systematic online search and expert consultations. Two researchers systematically searched Medline via PubMed, the web portal of the International Cancer Control Partnership (ICCP), and national (health ministry) websites for included countries between January 2010 and March 2022.

The search terms for PubMed constituted a combination of Medical Subject Heading (MeSH) terms and key words including but not limited to: Human papillomavirus vaccination, cervical cancer screening, cervical cancer prevention, non-communicable diseases control policy OR plan OR strategy OR guideline AND country name. Our search strategy on PubMed was:

(Human Papillomavirus vaccination OR cervical cancer screening OR cervical cancer prevention OR cancer

prevention OR non-communicable diseases prevention OR cervical cancer prevention OR cancer prevention OR non communicable diseases prevention) AND (policy or strategy or strategic plan or guidelines or report or directives) AND (Botswana OR Eswatini OR Lesotho OR Malawi OR Mozambique OR Namibia OR South Africa OR Zambia OR Zimbabwe) restricted between January 2010 and May 2019 and updated the search until March 2022. Search terms for health ministry websites included the country name, cervical cancer prevention, cancer prevention and non-communicable diseases control policy, plan, strategy, or guideline. For the ICCP portal, we identified cervical cancer, cancer and NCDs control plans, policies and strategies as well as WHO country profile reports. In addition, we contacted CC prevention and control experts from each included country and asked for any additional relevant documents. Experts from six countries were identified through sites visits conducted by SA within the context of the present study and other studies. Experts from the other three countries not visited (Eswatini, Botswana and Namibia) were recommended by a CC expert in South Africa. We identified global indicators from the Improving Data for Decision-making: a Toolkit for Cervical Cancer Prevention and Control Programmes [11] and the Comprehensive Cervical Cancer Control: a guide to essential practice [12].

Data charting and management

A data extraction sheet was developed by four researchers (SA, MD, KT and JB), reviewed and approved by the country experts. Data items extracted included policies and protocols related to primary, secondary and tertiary prevention, monitoring and evaluation mechanisms, and service costs to women. The full list of extracted data items is attached in the Additional file 5. We reported indicators for monitoring with a focus on global indicators for CC prevention and control as well as specifications for WLHIV. We also reported corresponding targets, and where available, benchmarks for global indicators. Data was extracted by one reviewer (SA) onto a piloted extraction sheet. All extracted data was cross-checked by a second reviewer (MD). All discrepancies were discussed and resolved.

Reports that were not available in English (documents from Mozambique were in Portuguese) were translated using a translation software, https://www.deepl.com/en/translator and a country expert validated all extracted information. In addition, we consulted one CC prevention expert from each included country for other information pertaining to their CC prevention programmes. We sent two short questionnaires to the experts. The first was a six-item questionnaire extracted from the WHO toolkit for CC prevention and control programmes [11] (Additional file 6). Questions focused on the existence and basic content of policies, plans, and guidelines relevant to CC prevention and control. The second was the WHO 11-item checklist for a comprehensive CC prevention and control program (Additional file 7). This checklist included items on the availability of guidelines for CC prevention specific to WLHIV, availability of financial and technical resources to implement policies, communication strategies to educate the community and advocate for support of national policies, availability of a training plan as well as supervisory mechanisms for quality control and assurance of the programme.

Data synthesis

We summarised results under five main subheadings: HPV vaccination, sex education, condom use, voluntary medical male circumcision (VMMC) and tobacco control (primary prevention); screening and treatment for cervical pre-cancer lesions (secondary prevention), cervical cancer treatment (tertiary prevention), monitoring and surveillance mechanisms, and costs of services.

The protocol of this review (initially conceived as a scoping review) is registered as a preprint on the African Open Access Portal [13].

Changes to the protocol

We revised our study design from a scoping review to a systematic review. Consequently, we used the PRISMA guidelines for systematic reviews for reporting and not the PRISMA guidelines for scoping reviews (PRISMA-ScR) as defined in the protocol. Contrary to the exclusion criteria stated in the protocol, ("we will exclude general cancer control plans where a recent standalone CC prevention and control document is available"), we included other cancer, NCD and national plans that contained some information on CC prevention even where there was a standalone policy. Additionally, we contacted country experts for CC prevention policies and related documents. We did not extract definitions of CC indicators as stated in the protocol. We revised our objective and extracted more detailed information on primary, secondary and tertiary prevention of CC as defined by included countries.

Results

We identified nine countries in SSA with HIV prevalence $\geq 10\%$ in 2018: Botswana, Eswatini, Lesotho, Malawi, Mozambique, Namibia, South Africa, Zambia, and Zimbabwe. We identified and reviewed 33 policy documents (Additional file 9). A PRISMA flowchart summarising the document selection process is presented in Fig. 1.

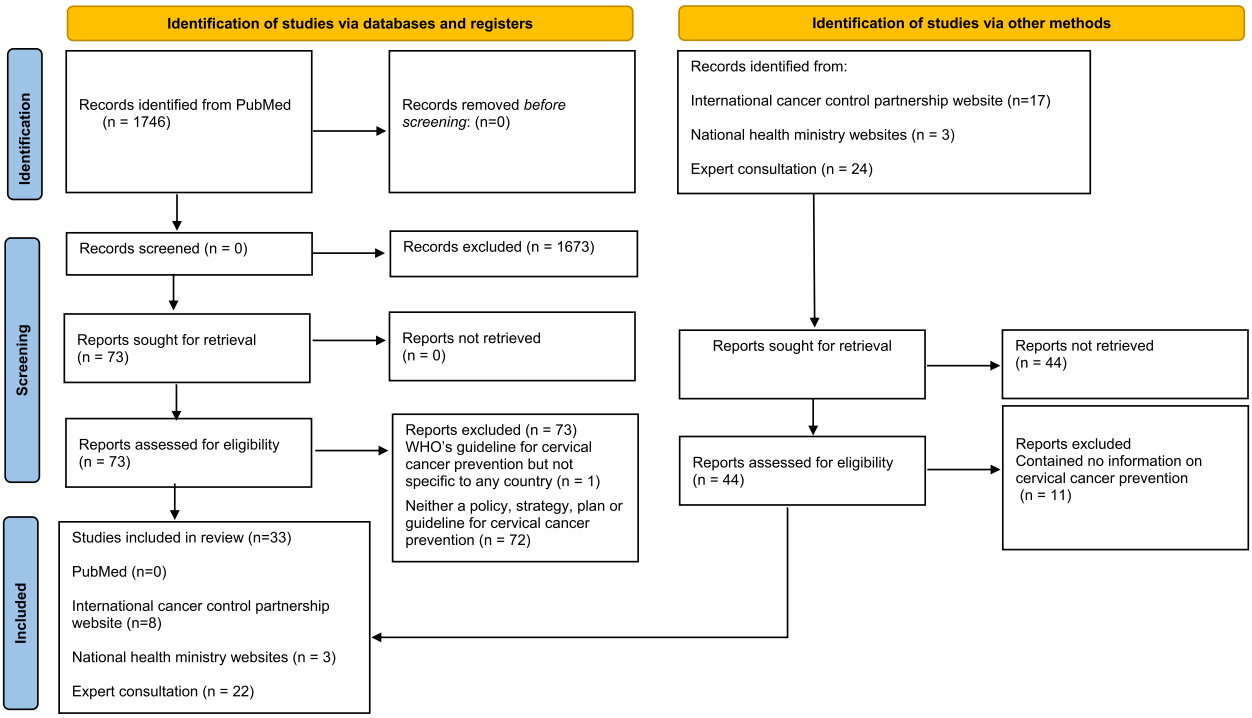

Fig. 1 PRISMA flow chart for study selection

HPV vaccination, sex education, condom use, voluntary medical male circumcision and tobacco control (primary prevention)

Seven countries reported some aspects of HPV vaccination in their policy documents. Girls between 9–13 years old was the target population for vaccination reported in three of the six countries that defined this item in their policy documents [14, 15]. Reports did not include boys as a target population for vaccination. The school-based vaccination strategy was reported by over a third of the countries (Botswana, Malawi, Namibia and South Africa) [16–21]. Also, two countries had integrated HPV vaccination in the national vaccination programme (Botswana and South Africa) and one was conducting a demonstration programme (Zimbabwe) [22, 23]. Malawi and Zambia were planning to introduce HPV vaccination in the national immunization programme. Only Namibia and Malawi included specifications for HPV vaccination for girls living with HIV in the reviewed documents (Table 1). A three-dose schedule for HPV vaccination was recommended over a 2-dose schedule for the general population of girls [21, 24]. All countries highlighted the need to develop/revise IEC materials for CC prevention. Sex education and warnings about tobacco use were recommended by all countries [15, 16, 22, 24–30]. Condom use was recommended by all countries for the prevention of sexually transmitted infections including HPV [16, 21, 24, 27–29, 31, 32]. In Lesotho and Namibia, we found specific recommendations for condom use.

within two weeks after pre-cancer treatment [24, 27]. The promotion of VMMC was highlighted in policy documents in Malawi, South Africa, Namibia and Botswana [20, 28, 33–35] (Additional file 1).

Screening for and treatment of cervical pre-cancer lesions (secondary prevention)

Most countries recommended cervical screening for WLHIV. The recommended age to start cervical screening for WLHIV varied across countries and differed from the general population in all countries. Zimbabwe recommended starting screening at HIV diagnosis irrespective of age; Namibia recommended starting at 20 years; Lesotho, Malawi and Zambia recommended starting at age 25 years; while Mozambique, and South Africa recommended screening for all ages irrespective of HIV diagnosis [24, 27, 29, 31, 32, 35–38]. There was no information on target age for screening in the general population of women or WLHIV in policy documents in Eswatini. Visual Inspection with Acetic acid (VIA) and Pap smear were the most commonly recommended tests for cervical screening and both were reported in all countries except for Mozambique and Zambia (only VIA reported) [39, 40]. However, the expert in Mozambique we consulted reported that visual inspection with Lugol's iodine

Table 1 Human Papillomavirus (HPV) Vaccination

Country	Target population	Target age (years)	Vaccination strategy	Specifications for girls living with HIV	Integrated in national HPV immunization programme
Botswana	Girls	11–13	School-based	NR	Implemented
Eswatini[a]	NR	NR	NR	NR	NR
Lesotho[a]	NR	9–13	NR	NR	NR
Malawi[a]	Girls	9–14 10 (out-of-school)	School and health facility-based	3-dose vaccination schedule	Recommended
Mozambique	NR	NR	NR	NR	NR
Namibia	Girls	9–14	School-based	3-dose vaccination schedule	NR
South Africa	Girls	9–12	School-based	NR	Implemented
Zambia	Girls	9–13	NR	NR	Recommended
Zimbabwe	Girls	10[b]-14 in school and 10 out of school	NR	NR	Implemented (during demonstration programme)

NR is Not Reported

[a] Vaccination not available in these countries (expert response)

[b] Estimated age (reported in policy document as grade 5)

Table 2 Cervical screening, diagnosis and treatment of precancerous lesions

Country	Target age group [years]	Specifications for WLHIV	Entry point	Screening method	Available diagnostic procedures	Treatment of precancerous lesions
Botswana	30–49	NR	NR	VIA, Pap smear, HPV DNA	Colposcopy and histopathology	Cryotherapy, LEEP
Eswatini	NR	NR	Integration into existing services recommended	VIA and Pap smear	Histopathology[b]	Cryotherapy, LEEP, TAH
Lesotho	25–49	Start at HIV diagnosis; Freq.—1 year	NR	VIA, VILI, Pap smear, HPV DNA testing	Not available	Cryotherapy, cold coagulation, LEEP
Malawi	25–49	Start age 25 21–24 upon request Freq.—2 years	HIV clinic, SRH	VIA, Pap smear, HPV DNA testing	Histopathology	Cryotherapy, cold coagulation, surgery, LEEP
Mozambique	NR	Screen all ages	Integration of HIV and CC screening services recommended	NR[a]	Histopathology	Cryotherapy, surgery
Namibia	25–50	Start at age 20	HIV clinics, ANC clinics	VIA, Pap smear, HPV DNA testing	Colposcopy and histopathology	Cryotherapy, LEEP, Thermocoagulation
South Africa	30–55	Screen all ages	Family planning, HIV clinic	LBC, Pap smear, VIA, HPV DNA testing	Histopathology	LEEP, Cryotherapy for low-resource settings
Zambia	30–59	Start age 25	HIV clinic, MCH	VIA	Histopathology	Cryotherapy, LEEP
Zimbabwe	30–49	Start at HIV diagnosis; Freq.—1 year	Family planning, maternity, Gynaecological clinics, HIV clinics	VIAC, Pap smear[c]	Histopathology	Cryotherapy, LEEP

ANC is Antenatal clinic, *MCH* is Mother and Child Health clinic, *SRH* is Sexual and Reproductive Health unit, *Freq.* is frequency, VIA is Visual inspection with acetic acid, *VILI* is Visual Inspection with Lugol's Iodine, *LBC* is Liquid based cytology, *LEEP* is Loop electrosurgical excision procedure, *LLETZ* is Large loop excision of the transformation zone, *TAH* is Total abdominal hysterectomy *NR* is Not reported

[a] VILI, Pap, HPV DNA testing (expert report)

[b] Expansion of services ongoing

[c] Pap smear mostly done in private health facilities

(VILI), Pap and HPV DNA testing are used (Table 2). HPV DNA testing was also recommended in policies in Botswana, Lesotho, Malawi, Namibia, and South Africa. Eight countries reported having histopathology as part of diagnostic services (Table 2). Lesotho did not report any pathology services. Treatment, by cryotherapy or LEEP, was reported in all countries. Eswatini also reported total abdominal hysterectomy for the treatment of cervical precancerous lesions [41]. Cervical screening services were integrated into HIV clinics in Malawi, Namibia, South Africa, Zambia, and Zimbabwe. Integration of cervical screening into HIV clinics and existing services was recommended in Mozambique and Eswatini, respectively [26, 29] (Table 2). The recommended cervical screening interval for WLHIV who screened negative varied between one year (Zimbabwe), two years (Malawi, Lesotho), and three years (Namibia, South Africa, and Zambia). Three countries did not report on this data item. This interval was wider for HIV negative women and varied from three years (Lesotho, Malawi, and Zimbabwe), five years (Namibia, Zambia and Lesotho (for women aged 50 years and older) to ten years in South Africa. Post-treatment follow-up at one year for WLHIV was recommended by Lesotho Malawi, Namibia, South Africa, Zambia, and Zimbabwe. In Malawi and Namibia, routine screening would resume after three negative annual screening while in South Africa, annual screening continued until the woman is lesion free before routine screening was resumed (Table 3).

Treatment of invasive cervical cancer (tertiary prevention)

Available treatment services for invasive CC were reported in six countries: surgery (South Africa, Malawi, radiotherapy (Botswana, Mozambique, Namibia, South Africa, Zambia, and Zimbabwe) and chemotherapy (Botswana, Malawi, South Africa and Zambia). Palliative care was reported available in seven countries; Additional file 2). Lesotho reported the need to have treatment services available in-country. Women diagnosed with invasive cancer were referred to South Africa for treatment [27].

Monitoring and surveillance mechanisms

Data systems were either paper-based (Lesotho, Malawi, Mozambique) or a combination of electronic and paper-based (Botswana, Namibia, South Africa, Zambia). Eswatini reported transitioning to an electronic data system while Zimbabwe did not explicitly state the nature of their data collection system (Table 4). We checked whether the countries report the four global indicators recommended by the WHO for monitoring CC elimination progress: HPV vaccination coverage, screening rate, screening test positivity rate and treatment rate, and whether these indicators were disaggregated by HIV status (Table 5). We also identified and reported corresponding national targets and/or benchmarks for these indicators, when available. All countries defined indicators for monitoring CC prevention and control programmes, and we listed them in (Additional file 8). At least two global indicators were reported in all countries except Eswatini. Only four countries reported these indicators explicitly disaggregated by HIV status. Five other national indicators recommended by Zimbabwe were also disaggregated by HIV status. The number of WLHIV screened for precancerous lesions was reported in Botswana, Malawi and Namibia. VIA test positivity was

Table 3 Post screening/treatment follow-up

Recommended rescreening interval				
Country	**Screen negative**		**After treatment**	
	HIV negative	**HIV positive**	**HIV negative**	**HIV positive**
Botswana	NR	NR	NR	NR
Eswatini	NR	NR	NR	NR
Lesotho	3–5 years	2 years	1 year post treatment then return to routine screening	6 months post treatment then yearly screening thereafter
Malawi	3 years	2 years	Yearly for 3 years then return to routine screening	
Mozambique	NR	NR	NR	NR
Namibia	5 years	3 years	Yearly for 3 consecutive years then return to routine screening	Yearly for 3 consecutive years then return to routine screening
South Africa	10 years	3 years	Yearly	Yearly until lesion-free then return to routine screening
Zambia	5 years	3 years	NR	Yearly
Zimbabwe	3 years	yearly	1 year post treatment	1 year post treatment

NR is not reported

Table 4 Monitoring and surveillance systems

Country	Referral system	Data system	Cancer register
Botswana	Available	Electronic and paper-based	Available
Eswatini	Lack of referral system	Transition to electronic data collection ongoing	Available
Lesotho	System available with referral logbook	Paper based	NR[c]
Malawi	Structured system with algorithm	Paper based	Available
Mozambique	NR[b]	Paper based	Available
Namibia	Available	Electronic and paper based	Available
South Africa	Structured system	Electronic and paper based	Available
Zambia	Design of referral systems recommended	Electronic and paper based	Available
Zimbabwe	Not fully functional	NR[a]	Available

NR is not reported

Experts' reports:

[a] Available but needs strengthening;

[b] Not available;

[c] Not available

disaggregated by HIV status in Botswana, Mozambique and Namibia. Treatment rate by HIV status was reported in Botswana and Namibia. Other recommended national indicators disaggregated by HIV status were: percentage of health facilities providing integrated HIV/sexually transmitted infections (STI)/CC screening, number of staff trained in integrated CC/breast/HIV/STI service per facility, percentage of facilities with HIV/STI and cancer integrated services, percentage of clients accessing integrated HIV/STI and cancer services, number of staff trained in integrated cancer/HIV/STI early detection and management services. Targets were defined for the general population of women, with no specificities for WLHIV. There were no details in reviewed documents describing how these targets were arrived at. In Malawi however, their updated guideline included a revised target for screening coverage from 80 to 70% "to reflect WHO targets" [21]. Targets for HPV vaccination ranged from 80% (Zambia and Zimbabwe) to 100% (South Africa). Targets for screening coverage ranged from 65% (South Africa) to 80% (Botswana, Malawi, Mozambique, Namibia). Zambia defined a benchmark of 5–10% test positivity rate for screened women. Treatment coverage targets ranged between 80% (Botswana, Zambia for treatment of cervical precancerous lesions by cryotherapy and treatment of CC) and 95% (Zambia for LEEP). Cancer registries were present in all countries but Lesotho [15, 21, 28–30, 33, 37, 42]. CC data registration was done in all eight countries although with some limitations. Most registries were not population-based (Malawi, Eswatini, Zambia, and/or located only in major cities (Zimbabwe, Mozambique). Malawi highlighted the need to enhance linkages between the CC prevention programme and the cancer registry while Eswatini recommended strengthening cancer data registration. Zambia sought to strengthen cancer registration by making cancer a notifiable disease and expanding from hospital-based registries to population-based.

Costs of services to women

Three countries reported the costs of HPV vaccination in their policy documents. This service was free of charge in Malawi and in government facilities in Lesotho. In South Africa, HPV vaccination was free only in schools. Cervical screening services were free in Lesotho, Malawi, South Africa, Mozambique and Namibia (expert report) and free for vulnerable groups in Botswana. Diagnostic services were free for vulnerable groups in Botswana and in public facilities in South Africa. These services were paid for by women in Zimbabwe and were expensive (expert report, Additional file 3). Treatment for cervical precancerous lesions was free in Malawi and South Africa, for vulnerable groups in Botswana, and in some health facilities in Zimbabwe. Treatment for invasive CC was free in public health facilities in South Africa while these services were unaffordable in Zimbabwe (Additional file 3). Other countries did not report on costs of treatment.

Discussion

In this review, we evaluated and summarised policies and recommendations for CC prevention and control in the nine SSA countries with the highest HIV prevalence. All countries reviewed had cancer control policies containing aspects of CC prevention. There was considerable variation in the surveyed countries' recommendations

Table 5 Indicators and targets for cervical cancer prevention and control

Country	WHO global indicators				Country targets					
	Vaccination rate	Screening rate	Screening test positivity rate	Treatment rate	Vaccination coverage	Timeline	Screening coverage	Timeline	Treatment coverage	Timeline
Botswana	✓	✓[a]	✓[a]	✓[a]	98%	2025	80%	2022	80%	2022
Eswatini	X	X	X	X	X	X	X	X	X	X
Lesotho	✓	✓	✓	✓	90%	X	X	X	X	X
Malawi	✓	✓[a]	✓	✓	95%	2026	70%	2026	85%	2026
Mozambique	X	✓	✓[a]	X	X	X	80%	X	X	X
Namibia	✓	✓[a]	✓[a]	✓[a]	95%	X	80%	2025	X	X
South Africa	✓	✓	✓	✓	100%	✓	65%	X	X	X
Zambia	✓	✓	✓	✓	80%	X	[b]5-10%	Monthly	80%:Cryotherapy: 95%:LEEP: > 80%:ICC treatment	80%
Zimbabwe	✓	✓	X	X	80%	2018	X	X	X	2020
	Other indicators disaggregated by HIV status									
Zimbabwe	Percentage of health facilities providing integrated HIV/STI/CC screening		Number of staff trained in integrated CC/breast/HIV/STI service per facility		Percentage of facilities with HIV/STI and cancer integrated services				Percentage of clients accessing integrated HIV/STI and cancer services	
			Number of staff trained in integrated cancer/HIV/STI early detection and management services							

[a] Disaggregation of data point by HIV status

[b] Test positivity benchmark for new women screened; WHO's timeline for 70–90-70 targets is 2030

for CC prevention among WLHIV. The most common reported age group for HPV vaccination was 9–13 years, with specific considerations for girls/women living with HIV recommended in Namibia. The school-based strategy was the most common vaccination strategy. Integration of HPV vaccination into national immunisation programmes was less common. Sex education, promotion of condom use for sexually active individuals and warnings against tobacco use was recommended in all countries, while VMMC was recommended in four countries. Age to start cervical screening varied across policies. Dominant reported methods for cervical screening, pre-cancer diagnosis, and treatment were VIA, Pap smear testing, histopathology, cryotherapy, and LEEP. Cervical screening was mostly integrated into gynaecological units, HIV clinics, family planning units, and mother and child health units and was not always free of charge. Invasive CC treatment recommendations for WLHIV were not common in the policies reviewed. Data systems for monitoring were widely available in the countries studied. There was a general lack of HIV-disaggregated indicators for monitoring.

Comparison with WHO guidelines and current evidence

The most common age group reported for HPV vaccination in policy documents lies within WHO's recommended age group for HPV vaccination, i.e. 9–14 years [8]. However, the WHO's suggestion that HPV vaccination should be implemented within national immunisation programmes was not commonly practised by the countries we surveyed. A recent report on HPV vaccination programmes in LMICs showed that five of the countries included in this review (Malawi, Zambia, Zimbabwe, Botswana, and South Africa) had introduced HPV vaccination, partially or nationwide [43] which corresponds to information extracted from their policy documents. The Vaccines in National Immunisation Programmes report of 2019, indicated that four of these countries (Botswana, South Africa, Zambia, and Zimbabwe) had integrated HPV vaccination in their national immunisation programme [44], which also corroborated their policy documents. The exception to this trend was Zambia, which reported this aspect as 'recommended' [15]. These disparities in reports between country policy documents and other published reports may be explained by changes in practice not yet captured in these documents. We found specific recommendations for HPV vaccination for girls living with HIV only in Namibia and Malawi. Recent evidence suggests that a one-dose vaccination schedule for girls in the general population is effective against persistent HPV infection [45]. For girls living with HIV, whether the number of doses can be reduced to two remains unclear. However, WHO suggests to continue with three doses [46]. Although HPV vaccination has been shown to be beneficial in reducing incidence rates of all HPV-related disease among the female and male populations [47, 48], vaccination for boys may not be the best investment in limited health care resources contexts [49, 50]. Limited financial resources was highlighted in policy documents in Malawi, Mozambique, Namibia and South Africa as a barrier to extension of vaccination services to boys [16, 21, 28, 29]. The school-based vaccination strategy has also been shown to achieve higher coverage compared to other strategies [43]. Consistent condom use and VMMC offer some protection against HPV transmission [51–55]. There is also evidence that consistent condom use improves the chances of regression of cervical intraepithelial neoplasia [56]. Both primary prevention methods are recommended by WHO for the prevention of HIV and other STIs [57, 58]. Smoking negatively affects HPV disease progression [59]. Tobacco use reduction is one of WHO's "best buys" for primary prevention of NCDs including CC [60]. All countries aligned their tobacco control policy with WHO's Framework Convention for Tobacco Control (FCTC), recommending price and tax measures to reduce demand for tobacco, bans on advertising and sponsorship as well as education, and public awareness amongst other strategies [61]. The WHO recommends that WLHIV are screened with the HPV DNA test rather than VIA or cytology [8]. While HPV DNA testing was available in five countries, VIA and cytology were the most common tests used. These results are consistent with those reported in a review of policies in East African countries where the CC burden is also high [62]. Lesotho, Malawi and Zambia advise commencing screening from 25 years for WLHIV, which aligns with WHO's updated recommendations [8]. There is also a need to balance cost-effectiveness with the socio-cultural specificities of a given country. For example, Mozambique and South Africa advise screening WLHIV of all ages which may not be cost-effective but may be advisable given the tendency for early sexual debut [63, 64]. Treatment of CC in WLHIV also requires some considerations as chemo radiation in immunocompromised women (including WLHIV) may pose some challenges [65]. The increased risk of recurrent infection after treatment in WLHIV also requires shorter follow-up intervals compared to women in the general population [8]. The WHO provides guidance for disaggregating monitoring indicators by HIV status, to identify gaps for this vulnerable population and corrective measures for prevention and control programmes [11]. Monitoring cervical screening in LMICs is challenging. One of the major barriers is the lack of

formal screening registries used in high-income countries such as England, Australia, and New Zealand [66]. Electronic systems for data collection were less common in the countries studied. These systems reduce cost and time for data collection, management, and patient monitoring [67]. In several SSA countries, the predominance of paper-based monitoring systems limits the collection of comprehensive CC data including indicators disaggregated by HIV status. Also, national CC prevention and control activities are usually dispersed across different bodies or units (like NCDs and sexual and reproductive health) without centralised data systems, making monitoring even more complex and challenging [6]. For example, a recent mid-term review of Zimbabwe's CC prevention and control strategy revealed that there was no data on the proportion of women who ever tested for CC, which existed nationally, and data on investigations were not routinely collected at the national level [68].

The WHO also recommends integrating HIV and CC services. This will allow service providers to increase their skills and knowledge, improving care for a high-risk population and at the same time reducing stigma, and improving cost-effective use of resources [69, 70].

Funding for CC prevention is limited which implies that CC prevention services are not always free [66], creating a barrier to access. This could be addressed through strengthening partnerships with organisations such as UNAIDS, the International Atomic Energy Agency and the Go Further partnership to end AIDS.

Strengths and weaknesses

Our analysis was strengthened by the exhaustive search and data collection achieved. We supplemented online searches with policy documents, published and unpublished, and direct communication with country experts. We reported data items and indicators that present the full continuum of CC prevention and care.. We only reported indicators disaggregated by HIV status as seen in policy documents. However, in practice, some programmes, especially those integrated in HIV care, probably collect CC and HIV data with the ability to report indicators for WLHIV. Additionally, our focus on global indicators for monitoring progress toward CC elimination in this analysis does not account for indicators defined for subnational and national monitoring of CC prevention and control programmes. Furthermore, experts' responses may only reflect the programmes they work for and may not be representative of national practices. Some of the information collected through this systematic review process may have changed.

Conclusion

Many SSA countries are making strides with policy development and implementation for CC prevention and control. However, current national policies for CC prevention and control in SSA countries with a high HIV burden could be better tailored to the specific needs of women living with HIV. This review highlights gaps in CC prevention and control recommendations for WLHIV in nine SSA countries. To better adapt to the needs of WLHIV, these countries need to update their policies using the WHO's recent guidelines, while adapting them to context realities. Well defined indicators, appropriately disaggregated by HIV and monitoring all steps of CC continuum of care will further address gaps in CC control among WLHIV.

Abbreviations

AIDS: Acquired Immunodeficiency Syndrome; CC: Cervical Cancer; CIN: Cervical Intraepithelial Neoplasia; DNA: Deoxyribonucleic acid; HIV: Human Immunodeficiency Virus; HGSIL: High Grade Squamous Intraepithelial Lesion; HPV: Human Papillomavirus; ICCP: International Cancer Control Partnership; LBC: Liquid-Based Cytology; LEEP: Loop Electrosurgical Excision Procedure; LMICs: Low and Middle Income Countries; NCDs: Non Communicable Diseases; Pap test: Papanicolaou test; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SSA: Sub-Saharan Africa; STI: Sexually Transmitted Infections; UNAIDS: The Joint United Nations Programme on HIV/AIDS; VIA: Visual Inspection with Acetic Acid; VIAC: Visual Inspection with Acetic acid and Cervicography; VILI: Visual Inspection with Lugol's Iodine; WHO: World Health Organization; WLHIV: Women Living with HIV.

Supplementary Information

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Additional file 1. Other Primary prevention strategies (Sex education, condom use, circumcision and tobacco control)

Additional file 2. Treatment of invasive cervical cancer and palliative care

Additional file 3. Cost of services for clients

Additional file 4. Other responses from country experts (some questions from appendices 2 and 3)

Additional file 5. Data extraction sheet

Additional file 6. Extract from WHO's CC prevention and control toolkit for cervical cancer prevention and control programmes [11]

Additional file 7. WHO checklist for a comprehensive cervical cancer prevention and control programme [12]

Additional file 8. List of indicators and targets extracted from included policy documents

Additional file 9. List of documents reviewed

Additional file 10. Age standardised cervical cancer incidence and mortality rates for included countries

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Authors' contributions
SLA and JB designed the study. SLA searched for relevant publications, conducted the policy review, interpreted the results, drafted and finalised the manuscript. KT and MD participated in the study design. JB, KT and MD revised the tables and manuscript. MD searched for relevant publications and also conducted the policy review. All other authors (country experts) contributed to data collection and reviewed the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
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Declarations

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4.3. Publication 3

Cervical cancer prevention and care in HIV clinics across sub-Saharan Africa: results from a facility-based survey

Asangbeh-Kerman Serra Lem, **Davidović Maša**, Taghavi Katayoun, Dhokotera Tafadzwa, Manasyan Albert, Sharma Anjali, Jaquet Antoine, Musick Beverly, Twizere Christella, Chimbetete Cleophas, Murenzi Gad, Tweya Hannock, Muhairwe Josephine, Wools-Kaloustian Kara, Technau Karl-Gunter, Anastos Kathryn, Yotebieng Marcel, Jousse Marielle, Ezechi Oliver, Orang'o Omenge, Bosomprah Samuel, Boni Simon Pierre, Basu Partha, Bohlius Julia; International Epidemiology Databases to Evaluate AIDS

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Own contribution: I played a key role in the study's conceptualization and supported the first author in developing, piloting, and disseminating the survey, including assisting with the setup and pilot testing of the survey using RedCap electronic software. I contributed to data collection, analysis, and interpretation. Additionally, I critically reviewed and provided feedback on the initial and subsequent manuscript drafts, as well as the supplementary material.

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RESEARCH ARTICLE

Cervical cancer prevention and care in HIV clinics across sub-Saharan Africa: results of a facility-based survey

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Abstract

INTRODUCTION: To eliminate cervical cancer (CC), access to and quality of prevention and care services must be monitored, particularly for women living with HIV (WLHIV). We assessed implementation practices in HIV clinics across sub-Saharan Africa (SSA) to identify gaps in the care cascade and used aggregated patient data to populate cascades for WLHIV attending HIV clinics.

METHODS: Our facility-based survey was administered between November 2020 and July 2021 in 30 HIV clinics across SSA that participate in the International epidemiology Databases to Evaluate AIDS (IeDEA) consortium. We performed a qualitative site-level assessment of CC prevention and care services and analysed data from routine care of WLHIV in SSA.

RESULTS: Human papillomavirus (HPV) vaccination was offered in 33% of sites. Referral for CC diagnosis (42%) and treatment (70%) was common, but not free at about 50% of sites. Most sites had electronic health information systems (90%), but data to inform indicators to monitor global targets for CC elimination in WLHIV were not routinely collected in these sites. Data were collected routinely in only 36% of sites that offered HPV vaccination, 33% of sites that offered cervical screening and 20% of sites that offered pre-cancer and CC treatment.

CONCLUSIONS: Though CC prevention and care services have long been available in some HIV clinics across SSA, patient and programme monitoring need to be improved. Countries should consider leveraging their existing health information systems and use monitoring tools provided by the World Health Organization to improve CC prevention programmes and access, and to track their progress towards the goal of eliminating CC.

Keywords: cervical cancer prevention; HIV; monitoring; outcomes; prevention and care cascades; sub-Saharan Africa

Additional information may be found under the Supporting Information tab of this article.

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1 | INTRODUCTION

The World Health Organization (WHO) seeks to eliminate cervical cancer (CC) within this century, and has defined the "90-70-90" targets it expects countries to reach by 2030: 90% of girls must be vaccinated with an HPV vaccine by the time they are 15 years old; 70% of women screened with a high-performance test at 35 and 45 years; and 90% of women diagnosed with cervical pre-cancer or cancer should be treated [1]. To achieve these targets, countries that have a high HIV burden must adopt CC prevention strategies that meet the specific needs of girls and women living with HIV (WLHIV), since they are more susceptible to disease than HIV-negative girls and women [2, 3]. This requires health sector reform to deliver comprehensive prevention and care services, including expanding community awareness, biomedical and clinical interventions, improving quality assurance and monitoring mechanisms, and providing the financial and technical resources necessary to implement programmes [4, 5].

When nations implement preventive HIV and CC services that meet women's needs over time and across different levels of their health systems, uptake of screening services and clinical outcomes both improve. This integrated service delivery model has been adopted by several sub-Saharan African countries that have a high HIV burden [6–12]. But these programmes are too often opportunistic with low coverage, so gains in reducing CC incidence and mortality may wane over time. Permanent reduction in CC incidence and mortality like in high-income countries [13] must be monitored using routinely collected data that informs indicators. Without such data, countries cannot assess their progress, identify gaps and devise effective interventions against CC [1].

Previous studies reported pre-cancer treatment rates of 25.6% in WLHIV in a public hospital in South Africa, 76.2% in women regardless of HIV status in Zambia and 78% in WLHIV in one clinic in Zimbabwe [14–16]. A 2017 systematic review suggested an extension of screening options applied to HIV-negative women, to WLHIV, with more frequent follow-up [2]. These studies do not report on all three WHO elimination targets or on other aspects of a comprehensive CC prevention and control programme. CC prevention practices within HIV clinics are rarely described and facilities rarely report data necessary to monitor WHO targets for eliminating CC in WLHIV.

We set out to fill these gaps with a survey-based study to qualitatively assess the implementation of CC prevention services across sub-Saharan Africa (SSA) at the facility/site level and use aggregate patient data to quantitatively assess cascades for WLHIV attending HIV clinics with fairly advanced CC prevention programmes.

2 | METHODS

2.1 | Study design and setting

We conducted this facility-based survey between November 2020 and July 2021 at 30 HIV clinics in four African regions that participate in the International Epidemiology Databases to Evaluate AIDS (IeDEA) consortium. IeDEA is a global network that gathers and analyses routinely collected clinical data from children, adolescents and adults living with HIV across 240 HIV treatment and care sites (https://www.iedea.org/). The IeDEA regional principal investigators for central, East, southern and West Africa did a convenience sampling of 30 HIV clinics that offered CC prevention and control services on- or off-site, and had electronic or paper-based systems for data collection.

2.2 | Study participants

We collected data for HPV vaccination and cervical screening in the following four populations:

(a) HPV vaccination

(i) *Girls, adolescents/young WLHIV in care*: girls aged 9–14 years and/or adolescents or young women aged 15–26 years who had at least one HIV medical care visit in the clinic during the index year (the year for which data were reported);

(ii) *Girls and/or adolescents and young WLHIV eligible for HPV vaccination*: according to each site's eligibility criteria.

(b) Cervical screening

(i) *WLHIV in care*: 15 years old or older, who had at least one HIV medical care visit during the index year;

(ii) *WLHIV eligible for cervical screening*: according to each site's eligibility criteria.

We harmonized these definitions of girls and women in care to ensure data could be compared across sites in different countries.

2.3 | Survey development

We constructed a survey, which we based on both the International Agency for Research on Cancer CANscreen5 tool (https://canscreen5.iarc.fr/) and the WHO Toolkit for Cervical Cancer prevention and control programmes [17]. First, we organized a meeting with IeDEA principal investigators, data managers, and the CANscreen5 and WHO toolkit development team members to discuss the scope of the study, study population, site eligibility and index years for data collection. Second, the lead author (SLA-K) visited six participating sites to discuss the survey with programme teams, then revised it based on their input. The revised survey was programmed into Research Electronic Data Capture (REDCap 9.8.2), a web-based application used to create databases and projects. We offered the survey in English and French.

We qualitatively assessed CC prevention and care services across six domains: (1) respondent and site characteristics; (2) HPV vaccination; (3) CC screening, diagnosis, and treatment; (4) data collection and aggregation systems; (5) evaluations and audits; and (6) decision and referral support systems.

We analysed aggregated data routinely collected for HPV vaccination, cervical screening, diagnosis and treatment services offered to WLHIV in these sites. We prioritized the WHO global indicators [17] that had been reported and included HPV vaccination proportion (a key indicator in monitoring WHO targets for eliminating CC).

2.4 | Survey piloting and data collection

Between May and August 2020, we piloted the survey at two sites, one in West and one in East Africa, collected feedback and then revised the survey. Target respondents were CC prevention and control programme managers or health personnel involved in CC screening activities. We invited respondents via an email that included automatically generated links to the survey. Sites that had challenges using REDCap 9.8.2 printed the forms, filled them in by hand and submitted scanned copies through a secured email server. One researcher (SLA-K) manually entered scanned responses into REDCap 9.8.2 and another (MD) checked the entries. Site investigators could also check the accuracy of their site data and could query the lead author if they detected any problems.

Table 1. Respondent and site characteristics

Region (no. of sites) Variables	Central Africa (*n* = 7) *N (%)*	East Africa (*n* = 8) *N (%)*	Southern Africa (*n* = 9) *N (%)*	West Africa (*n* = 6) *N (%)*	Total (*n* = 30) *N (%)*
Respondent's role in the programme					
Data manager	5 (56)	0 (0)	4 (44)	0 (0)	**9 (30)**
Nurse	0 (0)	2 (100)	0 (0)	0 (0)	**2 (7)**
Physician	2 (22)	3 (33)	2 (22)	2 (22)	**9 (30)**
Programme manager	0 (0)	3 (38)	1 (13)	4 (50)	**8 (27)**
Research manager/assistant	0 (0)	0 (0)	2 (100)	0 (0)	**2 (7)**
Facility location					
Urban	7 (28)	7 (28)	5 (20)	6 (24)	**25 (83)**
Rural	0 (0)	1 (20)	4 (80)	0 (0)	**5 (17)**
Facility type					
Public	5 (23)	7 (32)	8 (36)	2 (9)	**22 (73)**
NGO	1 (20)	1 (20)	1 (20)	2 (40)	**5 (13)**
FBO	1 (100)	0 (0)	0 (0)	0 (0)	**1 (3)**
Other	0 (0)	0 (0)	0 (0)	2 (100)	**2 (7)**
Service integration					
Within ART clinic using existing staff	2 (14)	4 (29)	2 (14)	6 (43)	**14 (47)**
In another unit in hospital where ART clinic is located	4 (30)	3 (23)	6 (46)	0 (0)	**13 (43)**
Off-site	1 (50)	0 (0)	1 (50)	0 (0)	**2 (7)**
Screen and treat approach used[a]					
Yes	1 (4)	8 (35)	9 (39)	5 (22)	**23 (77)**
No	5 (83)	0 (0)	0 (0)	1 (17)	**6 (20)**
Unknown	1 (100)	0 (0)	0 (0)	0 (0)	**1 (3)**
Single visit approach used[b]					
Yes	2 (10)	5 (25)	7 (35)	6 (30)	**20 (67)**
No	5 (50)	3 (30)	2 (20)	0 (0)	**10 (33)**

Note: Total percentages are column percentages in bold, and percentages per region are row percentages.
Abbreviations: ART, antiretroviral therapy; FBO, faith-based organization; NGO, non-governmental organization.
[a]Treatment could be offered during another visit after screening.
[b]Screening and treatment are offered during the same visit.

2.5 | Statistical analyses

The primary outcomes of interest for our analysis were: the availability and use of CC prevention services; and the proportion of girls vaccinated, women screened, and/or treated for cervical pre-cancer and CC. We used descriptive statistics to report site characteristics and calculated percentages for each indicator. We used a changing denominator (target approach) to calculate the CC prevention and care cascade, in which all women who reach a given step comprise the denominator for each subsequent step. The target approach highlights retention gaps where they appear in cascades [18]. We assessed the association of facility characteristics (facility location, facility type, services integration, presence of non-governmental organization [NGO] support for CC prevention) and availability of patient-level data to inform key performance indicators using chi-square and Fischer's tests as appropriate. We reported outcomes for sites with data disaggregated by HIV status, if they included data for 10 or more eligible girls or women in care. We chose this low cut-off because many sites (especially sites that vaccinated girls) collected data on a few girls and women. Because there were few sites with sufficient data in any region, we typically reported data for the total number of sites (bolded column percentages in Tables 1–4 and Tables S1–S4). We report complete data for girls eligible for HPV vaccination, cervical screening, diagnosis, treatment and referral in Tables S6–S11. We qualitatively summarized and reported good practices observed during the site visits. All analyses were performed with Stata 16 SE (Stata Corp., College Station, TX, USA).

3 | RESULTS

3.1 | Sites and respondent characteristics

We included 30 sites across 14 countries in four SSA IeDEA regions: Burundi and Rwanda in central Africa; Kenya, Tanzania and Uganda in East Africa; Lesotho, Malawi, Mozambique, South Africa, Zambia and Zimbabwe in southern Africa; and Burkina Faso, Nigeria and Côte d'Ivoire in West Africa (Figure 1 and Table S12). The survey response rate was 100%.

Table 2. Organization of screening, demand generation and financing

Region (no. of sites)	Central Africa (*n* = 7)	East Africa (*n* = 8)	Southern Africa (*n* = 9)	West Africa (*n* = 6)	Total (*n* = 30)
Variables	*N (%)*	*N (%)*	*N (%)*	*N (%)*	***N (%)***
Nature of screening programme					
Pilot	1 (50)	0 (0)	1 (50)	0(0)	**2 (7)**
Routine care	6 (30)	7 (35)	7 (35)	0 (0)	**20 (67)**
Research project	0 (0)	2 (33)	0 (0)	4 (67)	**5 (17)**
Individual or team for screening coordination					
Yes	5 (20)	7 (28)	7 (28)	6 (24)	**25 (83)**
No	1 (33)	0 (0)	2 (67)	0 (0)	**3 (10)**
Unknown	1 (100)	0 (0)	0 (0)	0 (0)	**1 (3)**
Pilot before screening implementation					
Yes	0 (0)	4 (44)	1 (11)	4 (44)	**9 (30)**
No	5 (36)	3 (21)	4 (29)	2 (14)	**14 (47)**
Unknown	2 (29)	1 (14)	4 (57)	0 (0)	**7 (23)**
Pilot evaluated					
Yes, report published	0 (0)	2 (50)	0 (0)	2 (50)	**4 (13)**
Yes, report not published	0 (0)	1 (100)	0 (0)	0 (0)	**1 (3)**
No	0 (0)	0 (0)	0 (0)	1 (100)	**1 (3)**
Unknown	0 (0)	1 (33)	1 (33)	1 (33)	**3 (10)**
Screening policy available					
Yes	3 (13)	7 (30)	7 (30)	6 (26)	**23 (77)**
No	1 (33)	0 (0)	2 (67)	0 (0)	**3 (10)**
Unknown	3 (75)	1 (25)	0 (0)	0 (0)	**4 (13)**
Screening guideline available					
Yes	2 (10)	7 (33)	6 (29)	6 (29)	**21 (70)**
No	3 (50)	1 (17)	2 (33)	0 (0)	**6 (20)**
Unknown	2 (67)	0 (0)	1 (33)	0 (0)	**3 (10)**
Initiatives for population awareness by Health Ministry					
Yes	4 (17)	7 (30)	6 (26)	6 (26)	**23 (77)**
No	2 (67)	0 (0)	1 (33)	0 (0)	**3 (10)**
Unknown	1 (33)	0 (0)	2 (67)	0 (0)	**3 (10)**
Awareness approach					
Mass media campaign	1 (5.6)	7 (39)	5 (28)	5 (28)	**18 (78)**
Small media campaign	0 (0)	1 (14)	1 (14)	5 (71)	**7 (30)**
Group education	4 (24)	5 (29)	3 (18)	5 (29)	**17 (74)**
One-on-one education	0 (0)	3 (30)	3 (30)	4 (40)	**10 (44)**
Unknown	1 (100)	0 (0)	0 (0)	0 (0)	**1 (3)**
Invitation system for eligible population					
Yes	0 (0)	4 (50)	2 (25)	2 (25)	**8 (27)**
No	6 (30)	3 (15)	7 (35)	4 (20)	**20 (67)**
Unknown	1 (100)	0 (0)	0 (0)	0 (0)	**1 (3)**
Invitation method					
SMS	0 (0)	0 (0)	1 (50)	1 (50)	**2 (25)**
Phone calls	0 (0)	2 (50)	1 (25)	1 (25)	**4 (50)**
Home visits by health workers	0 (0)	1 (25)	1 (25)	2 (50)	**4 (50)**
Sensitization during consultation	0 (0)	0 (0)	0 (0)	1 (100)	**1 (13)**
Word of mouth	0 (0)	0 (0)	1 (100)	0 (0)	**1 (13)**
Through media (radio, TV), One-on-one education	0 (0)	1 (100)	0 (0)	0 (0)	**1 (13)**

(*Continued*)

Table 2. (Continued)

Region (no. of sites)	Central Africa (*n* = 7)	East Africa (*n* = 8)	Southern Africa (*n* = 9)	West Africa (*n* = 6)	Total (*n* = 30)
System to invite selected populations					
Not screened in previous round	0 (0)	5 (71)	1 (14)	1 (14)	**7 (23)**
High-risk populations only	1 (13)	3 (38)	4 (50)	0 (0)	**8 (27)**
No system	3 (25)	1 (8)	3 (25)	5 (42)	**12 (40)**
Unknown	2 (67)	1 (33)	0 (0)	0 (0)	**3 (10)**
High-risk criteria					
HIV positive	0 (0)	3 (75)	1 (25)	0 (0)	**4 (50)**
HIV positive with menstruation complications	1 (100)	0 (0)	0 (0)	0 (0)	**1 (13)**
Referred from ART clinic	0 (0)	0 (0)	1 (100)	0 (0)	**1 (13)**
Women with high-risk HPV	0 (0)	0 (0)	1 (100)	0 (0)	**1 (13)**
Government allocated budget for CC prevention					
Yes	0 (0)	5 (39)	5 (39)	3 (23)	**13 (43)**
No	5 (39)	2 (15)	3 (28)	3 (23)	**13 (43)**
Unknown	2 (50)	1 (25)	1 (25)	0 (0)	**4 (13)**
NGO support for health facility					
Yes	4 (16)	8 (32)	9 (36)	4 (16)	**25 (83)**
No	2 (50)	0 (0)	0 (0)	2 (50)	**4 (13)**
NGO support for cervical cancer prevention					
Yes	0 (0)	5 (39)	7 (54)	1 (8)	**13 (43)**
No	7 (41)	3 (18)	2 (12)	5 (29)	**17 (57)**
Vaccination free of charge (in sites currently offering vaccination or who did in the past)					
Yes	5 (29)	5 (29)	5 (29)	2 (12)	**17 (100)**
Diagnosis for pre-cancer and CC free of charge					
Yes	0 (0)	3 (38)	4 (50)	1 (13)	**8 (27)**
No	5 (39)	2 (15)	1 (8)	5 (39)	**13 (43)**
Partially	0 (0)	0 (0)	2 (100)	0 (0)	**2 (7)**
Unknown	2 (40)	2 (40)	1 (20)	0 (0)	**5 (17)**
Treatment for pre-cancer and cancer treatment free of charge					
Yes	1 (11)	2 (22)	6 (67)	0 (0)	**9 (30)**
No	4 (40)	0 (0)	1 (10)	5 (50)	**10 (33)**
Partially	0 (0)	3 (50)	2 (33)	1 (17)	**6 (20)**
Unknown	2 (50)	2 (50)	0 (0)	0 (0)	**4 (13)**

Note: Total percentages are column percentages in bold, and percentages per region are row percentages.
Abbreviations: ART, anti-retroviral therapy; CC, cervical cancer; HPV, human papillomavirus.

Most respondents were either data managers (30%), physicians (30%) or programme managers (27%). Most sites were public sector facilities (73%) in urban areas (83%; Table 1).

3.2 | Site-level data: qualitative indicators

3.2.1 | *HPV vaccination*

Seventeen of 30 sites (57%) had offered (*n* = 7, 23%) or still offered (*n* = 10, 33%) HPV vaccination (Table S1). Vaccination services had been discontinued due to lack of funding (*n* = 3, 43%), vaccination offered once a year (*n* = 2, 29%), low community acceptance and COVID-19 (*n* = 1, 14%), and completion of pilot/research study (*n* = 1, 14%). HPV vaccines were delivered mostly through a combination of school- and community-based (*n* = 6, 20%) strategies. Of the 10 sites that still provided HPV vaccination, nine sites targeted only girls aged under 15 years. Services were free in all sites that offered HPV vaccination.

3.2.2 | *Organizing cervical screening, demand generation and programme financing*

All included sites offered cervical pre-cancer screening. These services were often integrated into the HIV clinic and provided by existing staff (47%) or in another unit where the HIV clinic was located, within the larger facility (43%) (Table 1). About a quarter of the CC screening programmes were pilot programmes (*n* = 2, 7%) or research studies (*n* = 5, 17%). Mass media campaigns (78%) and group education (74%)

Table 3. Screening, triage and treatment of pre-cancerous lesions

Region (no. of sites)	Central Africa (*n* = 7)	East Africa (*n* = 8)	Southern Africa (*n* = 9)	West Africa (*n* = 6)	Total (*n* = 30)
Variables	*N (%)*	*N (%)*	*N (%)*	*N (%)*	***N (%)***
Eligibility					
All women on ART	2 (17)	3 (25)	5 (42)	2 (17)	**12 (40)**
Other age ranges in years					
15–55	1 (50)	0 (0)	1 (50)	0 (0)	**2 (7)**
18–65	0 (0)	0 (0)	0 (0)	3 (100)	**3 (10)**
30–50	0 (0)	1 (50)	0 (0)	1 (50)	**2 (7)**
>35	1 (100)	0 (0)	0 (0)	0 (0)	**1 (3)**
25–49	0 (0)	0 (0)	1 (0)	0 (0)	**1 (3)**
Sexually active	0 (0)	0 (0)	1 (0)	0 (0)	**1 (3)**
Screening tests used[a]					
Cytology	1 (11)	2 (22)	3 (33)	3 (33)	**9 (30)**
VIA	4 (16)	7 (28)	8 (32)	6 (24)	**25 (83)**
VIAC	0 (0)	1 (13)	6 (75)	1 (13)	**8 (27)**
VILI	1 (20)	1 (20)	0 (0)	3 (60)	**5 (17)**
HPV DNA	0 (0)	3 (25)	6 (50)	3 (25)	**12 (40)**
Triage test used[a]					
Cytology	0 (0)	2 (67)	1 (33)	0 (0)	**3 (10)**
HPV DNA	0 (0)	0 (0)	1 (50)	1 (50)	**2 (7)**
Colposcopy	0 (0)	2 (67)	1 (33)	0 (0)	**3 (10)**
VIA	0 (0)	3 (25)	6 (50)	3 (25)	**12 (40)**
Biopsy	0 (0)	1 (100)	0 (0)	0 (0)	**1 (3)**
None	3 (43)	1 (14)	1 (14)	2 (29)	**7 (23)**
Testing considerations for post-menopausal women					
Yes	1 (9)	4 (36)	2 (18)	4 (36)	**11 (37)**
No	4 (25)	3 (19)	7 (44)	2 (13)	**16 (53)**
Unknown	2 (100)	0 (0)	0 (0)	0 (0)	**2 (7)**
Tests used for post-menopausal women among sites with testing considerations					
Cytology, on-site	0 (0)	1 (25)	1 (25)	2 (50)	**4 (36)**
Cytology, referred	1 (17)	3 (50)	0 (0)	2 (33)	**6 (55)**
HPV DNA	0 (0)	0 (0)	1 (100)	0 (0)	**1 (9)**
Diagnosis available on-site					
Yes	0 (0)	4 (31)	4 (31)	5 (39)	**13 (43)**
No	7 (44)	3 (19)	5 (31)	1 (6)	**16 (53)**
Pre-cancer diagnosis					
Colposcopy	1 (11)	2 (22)	3 (33)	3 (33)	**9 (30)**
Histopathology	0 (0)	3 (27)	4 (36)	4 (36)	**11 (37)**
Cytology	0 (0)	0 (0)	0 (0)	2 (100)	**2 (7)**
Not available	3 (38)	3 (38)	2 (25)	0 (0)	**8 (27)**
Pre-cancer treatment[b]					
Cryotherapy	3 (16)	6 (32)	4 (21)	6 (32)	**19 (63)**
CKC	0 (0)	1 (13)	2 (25)	5 (63)	**8 (27)**
Thermocoagulation	0 (0)	3 (23)	6 (46)	4 (31)	**13 (43)**
Simple hysterectomy	3 (27)	2 (18)	1 (9)	5 (46)	**11 (37)**
LEEP	1 (6)	5 (29)	5 (29)	6 (35.3)	**17 (57)**
None	3 (100)	0 (0)	0 (0)	0 (0)	**3 (10)**

(*Continued*)

Table 3. (Continued)

Region (no. of sites)	Central Africa (*n* = 7)	East Africa (*n* = 8)	Southern Africa (*n* = 9)	West Africa (*n* = 6)	Total (*n* = 30)
Screening intervals for screen-negative women					
6 months	0 (0)	1 (100)	0 (0)	0 (0)	**1 (3)**
12 months	3 (19)	5 (31)	3 (19)	5 (31)	**16 (53)**
24 months	0 (0)	0 (0)	4 (80)	1 (20)	**5 (17)**
36 months	0 (0)	1 (50)	1 (50)	0 (0)	**2 (7)**
Unknown	4 (100)	0 (0)	0 (0)	0 (0)	**4 (13)**
5 yearly (if HPV available)	0 (0)	0 (0)	1 (100)	0 (0)	**1 (3)**
Re-screening interval after pre-cancer treatment					
6 months	3 (33)	3 (33)	2 (22)	1 (11)	**9 (30)**
12 months	0 (0)	2 (14)	7 (50)	5 (36)	**14 (47)**
Unknown	4 (80)	1 (20)	0 (0)	0 (0)	**5 (17)**

Note: Total percentages are column percentages in bold, and percentages per region are row percentages.
Abbreviations: CKC, cold knife conisation; HPV DNA, human papillomavirus/deoxyribonucleic acid; LEEP, bop electrosurgical excision procedure; VIA, visual inspection with acetic acid; VIAC, visual inspection with acetic acid and cervicography; VILI, visual inspection with Lugol's iodine.
[a]Some sites used more than one screening or triage test.
[b]More than one treatment method used.

were commonly used to raise demand. Although 83% of sites received financial support from NGOs, less than half of sites (43%) received NGO support specifically designated for CC prevention. Clients paid the total cost (43%) or part of the cost (7%) for diagnosis of suspected cervical pre-cancer or invasive cancer and the total cost (33%) or part of the cost (20%) for pre-cancer and cancer treatment (Table 2).

3.2.3 | *Cervical pre-cancer screening and pre-cancer treatment*

CC screening was provided on-site in 93% of facilities, and off-site in 7%. About an equal number of sites either screened women of any age (40%), or women between 15 and 65 years. The method commonly used to screen (83%) was visual inspection with acetic acid (VIA). HPV DNA testing (40%) and cytology (30%) were performed at less than half of the sites. The most commonly used triage test was VIA (40%). Histopathology (37%) and colposcopy (30%) were commonly used for pre-cancer diagnosis and usually conducted off-site (53%). Cryotherapy (63%), thermocoagulation (43%) and loop electrosurgical excision procedure (57%) were the most common pre-cancer treatment methods. The most common follow-up interval for screen-negative women and women treated for pre-cancer was 12 months (Table 3).

3.2.4 | *Diagnosis and management of invasive CC*

Invasive CC diagnosis (69%) and treatment (67%) services were available in about two-thirds of the sites (Table S2). Histopathology was the most common diagnostic tool (40%). Simple hysterectomy (37%), radical hysterectomy (53%), chemotherapy (43%) and radiation therapy (40%) were used in combination across sites. Only six (20%) sites reported consistent availability of opioids.

3.2.5 | *Laboratory testing and quality assurance*

Laboratory testing was done either for pre-cancer only (29%) (HPV DNA testing or cytology), invasive CC diagnosis only (12%) (pathology) or both (59%) (HPV DNA testing, cytology and pathology) (Table S3). Results turnaround time varied between 1 and 4 weeks (65%) in most sites. Quality assurance coordinators who ensured that the screening programmes met quality standards were available in a little over half of the sites (59%); corresponding guidelines were available in 70% of these sites, but in 48% of all sites. Accreditation systems were available in 33% of sites that offered HPV DNA testing and 20% of sites that provided pathology services.

3.2.6 | *Referral and tracking*

Referral for CC screening was most often sporadic (60%); with only 23% consistently referring women for CC screening (Table S4). Of the 25 sites that referred women for pre-cancer treatment, 40% did so systematically and 43% did so sporadically. Of the 26 sites that referred women for CC treatment, 70% did so systematically. Thirty percent and 47% of sites had no treatment infrastructure for pre-cancer and CC, respectively. Women who had been referred were usually tracked by phone calls (48%).

3.2.7 | *Surveillance systems and data collection*

The sites mainly relied on electronic data systems (90%) (Table 4); 7 of 10 sites that offered HPV vaccination collected related data, and half the sites collected some data on CC

Table 4. Surveillance systems and data collection

Region (no. of sites) Variables	Central Africa (*n* = 7) *N (%)*	East Africa (*n* = 8) *N (%)*	Southern Africa (*n* = 9) *N (%)*	West Africa (*n* = 6) *N (%)*	Total (*n* = 30) *N (%)*
Electronic system for data collection and management					
Yes	7 (26)	7 (26)	7 (26)	6 (22)	**27 (90)**
No (paper forms)	0 (0)	0 (0)	2 (100)	0 (0)	**2 (7)**
Level electronic system available					
National	7 (36.8)	2 (10.5)	5 (26)	5 (26)	**19 (63)**
Sub-national	0 (0)	2 (67)	1 (33)	0 (0)	**3 (10)**
National and Sub-national	0 (0)	3 (60)	1 (20)	1 (20)	**5 (17)**
Unknown	0 (0)	0 (0)	1 (33)	2 (67)	**3 (10)**
Electronic system for data aggregation and reporting available					
Yes	4 (36)	3 (27)	2 (18)	2 (18)	**11 (37)**
No	2 (13)	3 (20)	6 (40)	4 (27)	**15 (50)**
Unknown	1 (33)	1 (33)	1 (33)	0 (0)	**3 (10)**
Standardized national indicators for CC monitoring available					
Yes	3 (18)	5 (29)	5 (29)	4 (24)	**17 (57)**
No	2 (33)	0 (0)	2 (33)	2 (33)	**6 (20)**
Unknown	2 (33)	2 (33)	2 (33)	0 (0)	**6 (20)**
CC prevention and control data collected					
Yes	0 (0)	5(33)	6 (40)	4 (27)	**15 (50)**
No	6 (50)	2 (17)	2 17)	2 (17)	**12 (40)**
Unknown	1 (50)	0 (0)	1 (50)	0 (0)	**2 (7)**
Vaccination data collected in sites with ongoing or past programmes					
Yes	4 (67)	1 (17)	1 (17)	0 (0)	**6 (55)**
No	0 (0)	1 (20)	4 (80)	0 (0)	**5 (46)**
Key indicators defined in programme					
Number vaccinated	3 (43)	3(43)	1 (14)	0 (0)	**7 (70)**
Number screened	3 (14)	6 (29)	8 (38)	4 (19)	**21 (70)**
Number screened positive	3 (14)	6 (29)	8 (38)	4 (19)	**21 (70)**
Number further assessed	0 (0)	3 (38)	5 (63)	0 (0)	**8 (27)**
Number treated	1 (7)	3 (20)	8 (53)	3 (20)	**15 (50)**
Indicators for CC prevention linked to HIV status available					
Yes	1 (9)	2 (18)	5 (46)	3 (27)	**11 (37)**
No	4 (36)	1 (9)	3 (27)	3 (27)	**11 (37)**
Unknown	2 (40)	2 (40)	1 (20)	0 (0)	**5 (17)**
CC prevention and care data available for WLHIV					
Number screened	0 (0)	2 (20)	5 (50)	3 (30)	**10 (33)**
Number treated for pre-cancer	0 (0)	0 (0)	4 (67)	2 (33)	**6 (20)**
Number treated for CC	0 (0)	2 (33)	3 (50)	1 (17)	**6 (20)**
Linkage of CC screening data with PBCR					
Yes, linked to hospital registry	0 (0)	2 (40)	3 (60)	0 (0)	**5 (17)**
Yes, linked to PBCR	0 (0)	0 (0)	1 (33)	2 (67)	**3 (10)**
PBCR exists but data not linked	0 (0)	1 (33)	1 (33)	1 (33)	**3 (10)**
No cancer registry exists	2 (29)	1 (14)	2 (29)	2 (29)	**7 (23)**
Not collecting CC prevention data	6 (50)	2 (17)	2 17)	2 (17)	**12 (40)**
Client identification					
Unique national ID number/code	0 (0)	2 (67)	1 (33)	0 (0)	**3 (10)**
Unique national client health number/code	2 (67)	0 (0)	0 (0)	1 (33)	**3 (10)**
Disease-specific unique identifiers	2 (29)	2 (29)	0 (0)	3 (43)	**7 (23)**
Facility-specific client number assigned at the first visit	3 (20)	2 (13)	8 (53)	2 (13)	**15 (50)**
No use of ID numbers or codes	0 (0)	1 (100)	0 (0)	0 (0)	**1 (3)**

(*Continued*)

Table 4. (Continued)

Region (no. of sites) Variables	Central Africa (*n* = 7) *N (%)*	East Africa (*n* = 8) *N (%)*	Southern Africa (*n* = 9) *N (%)*	West Africa (*n* = 6) *N (%)*	Total (*n* = 30) *N (%)*
Data collected on cancer stage					
Yes, systematically	1 (9)	5 (46)	2 (18)	3 (27)	**11 (37)**
No or sporadically	0 (0)	0 (0)	6 (75)	2 (25)	**8 (27)**
Unknown	2 (50)	0 (0)	1 (25)	1 (25)	**4 (13)**
Do you collect data on survival?					
Yes	1 (14)	3 (43)	1 (14)	2 (29)	**7 (23)**
No	5 (25)	3 (15)	8 (40)	4 (20)	**20 (67)**
Unknown	1 (50)	1 (50)	0 (0)	(0)0	**2 (7)**

Abbreviations: CC, cervical cancer; PBCR, population-based cancer registry; WLHIV, women living with HIV.

screening. Most sites (70%, *n* = 10) used at least one of the WHO global monitoring indicators for CC elimination, usually the number of girls vaccinated by age 15 years (*n* = 10; 70%), number of women screened (*n* = 30; 70%) and number of women treated (*n* = 30; 50%). Thirty seven percent of sites specifically linked HIV status to existing indicators.

3.2.8 | *Aggregated data: monitoring indicators reported for girls eligible for HPV vaccination and women in care at HIV clinics*

Of the 30 included sites, 11 (37%) collected data for outcome assessment of girls living with HIV and WLHIV, including HPV vaccination, CC screening, pre-cancer and CC treatment; 37% (*n* = 11) collected some data, but did not disaggregate it by HIV status. Sites receiving financial support from NGOs were more likely to have aggregated patient data informing key performance indicators (73%) as compared to sites that did not have such support (27%) (Table S5).

3.2.9 | *HPV vaccination*

Of the 10 sites that currently offered HPV vaccination, two reported HPV vaccination proportions for 10 or more girls living with HIV and eligible for HPV vaccination at their facility (Table S6); 21% of eligible girls were vaccinated in Newlands Clinic (Zimbabwe), and 88% in Kisesa (Tanzania).

3.2.10 | *Cervical pre-cancer screening*

Of the 15 sites that reported collecting data on cervical screening, only 11 had disaggregated indicators by HIV status (Table 4). Cervical screening proportions ranged from 4% in Hôpital de Jour du CHU Souro Sanou (Burkina Faso) to 78% in Newlands Clinic (Zimbabwe) (Figure 2, Panel a).

3.2.11 | *Pre-cancer treatment and CC management*

Pre-cancer treatment proportions were reported in 10 sites, ranging from 14% in Kanyama Hospital (Zambia) to 100% in George Health Centre (Zambia) (Figure 2, Panel b). Across all sites, there were wide disparities in attrition (proportion of women who did not reach the next necessary step of the cascade) between women whose screens were positive and those who were treated for pre-cancer, ranging from 0% in George Health Centre to 86% in Kanyama Hospital (Table S8). Only two sites reported data on the number of WLHIV who initiated treatment for CC; three women in Newlands Clinic (Zimbabwe), and one woman in Hôpital de Jour du CHU Souro Sanou (Burkina Faso) (Table S9).

3.2.12 | *Qualitative summary of good practices*

We visited six HIV clinics and two research centres mainly in southern Africa, and recorded some good practices. These included dedicated units and staff for screening, free treatment of precancerous lesions, task shifting for screening and pre-cancer treatment, capacity enhancement for pathology, unique patient identification, data linkages and partnerships (see Supplement 13 for details).

4 | DISCUSSION

We surveyed 30 HIV clinics across 14 countries in four SSA IeDEA regions to learn how they implemented CC prevention and care and to populate indicators with routinely collected patient data. Programmes for HPV vaccination were ongoing in only a third of the sites. Less than half of sites always referred women for pre-cancer and invasive CC diagnosis and treatment, at a fee for women. Almost all sites used electronic systems to collect data, though only half routinely collected CC data, including data needed to inform WHO global monitoring indicators for CC elimination.

WHO recommends HPV vaccination for primary prevention of CC and 41% of WHO member states in the African region had introduced HPV vaccination in their national immunization programmes by the end of 2019 [19]. By the time we conducted our study, some sites ceased vaccinating girls and women against HPV acquisition due to the COVID-19 pandemic and because of limited financial resources dedicated to HPV vaccination. These findings align with earlier studies that identified barriers to HPV vaccination [20, 21]. GAVI, the Vaccine Alliance, has been trying to address financial barriers for over a decade but funding challenges persist. Although the GAVI model has helped reduce financial barriers, countries

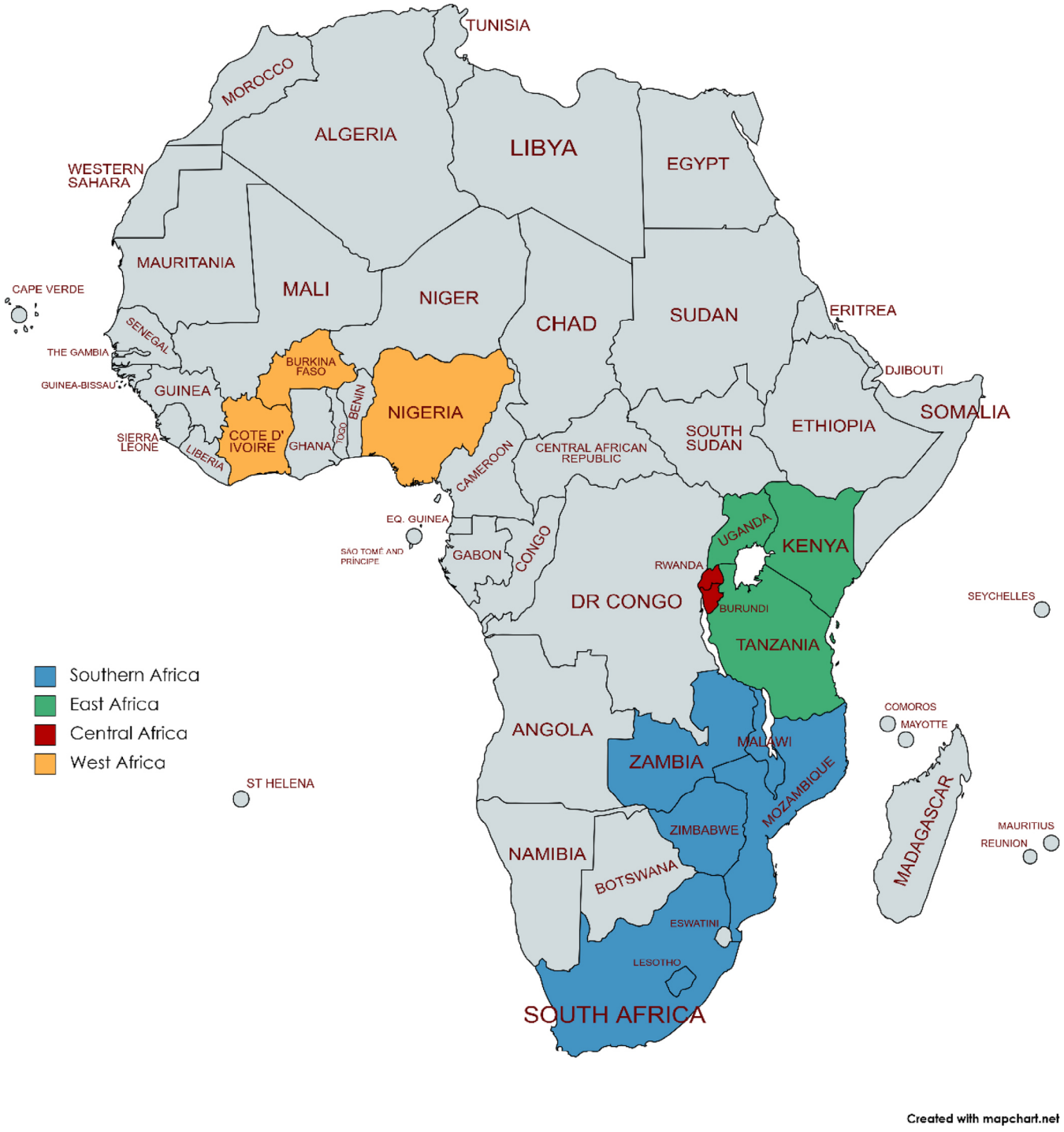
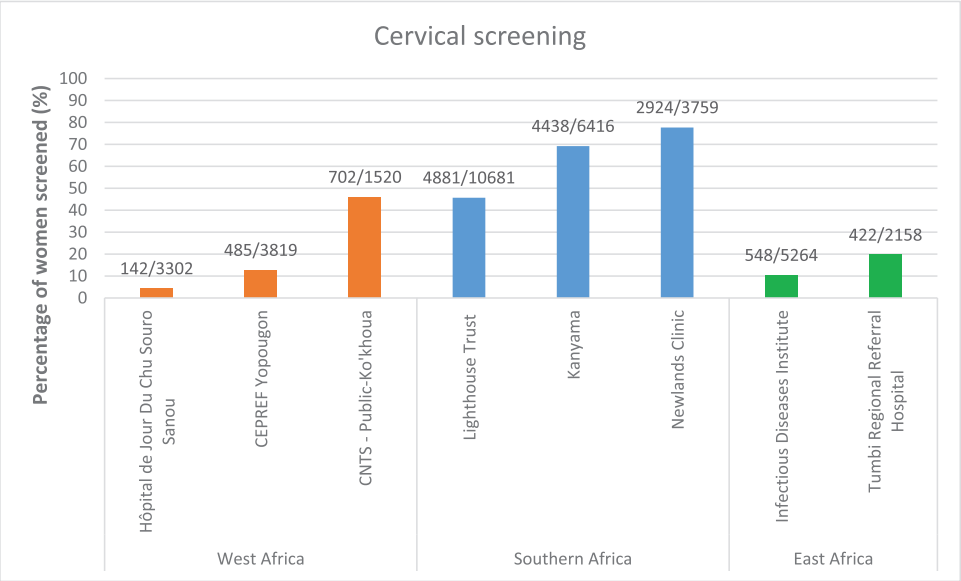


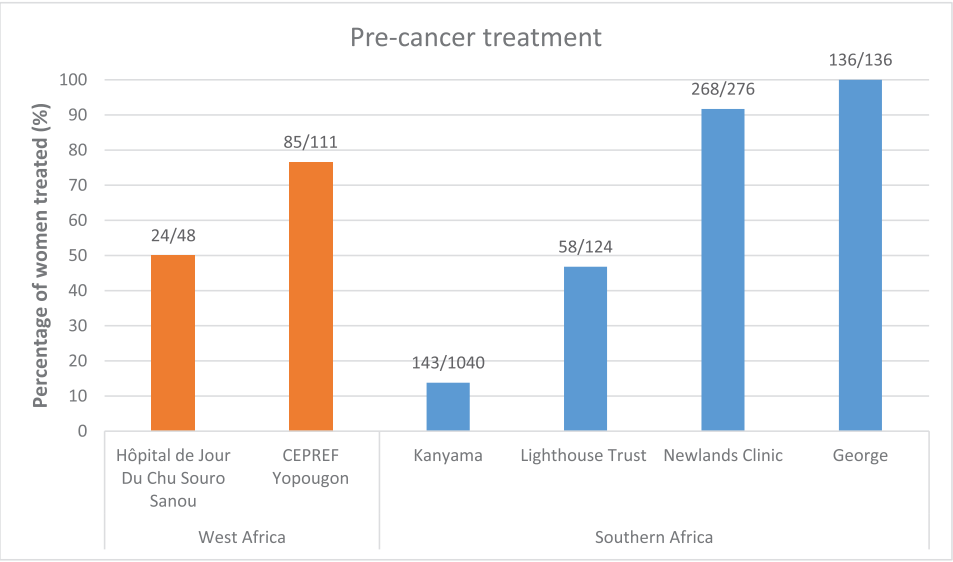
Figure 1. Map showing participating countries.

must commit to sustaining HPV vaccination programmes as they mature.

The repercussions of the COVID-19 pandemic are still not clear, but few reports attribute significant interruptions in vaccination programmes to the COVID-19 pandemic [22, 23]. We found little data on HPV vaccination for girls living with HIV and no previous published studies reported these estimates. Few studies reported data on HPV vaccination rates in the general population and data from countries in SSA are scarce [19, 24]. Since girls living with HIV may receive their booster vaccinations through school-based programmes, stigma could increase reluctance to get vaccinated and to report. This underserved population may benefit from innovative strategies to deliver vaccines and capture data, and all



Panel (a) Percentage of women in care screened by site and region



Panel (b) Percentage of women in care treated for pre-cancer by site and region

Figure 2. Percentage of women screened for cervical pre-cancerous lesions (Panel a) and percentage of women treated for cervical pre-cancer (Panel b). CEPREF, Centre de Prise en charge, de Recherche et de Formation; CNTS, Centre National de Transfusion Sanguine.

girls could benefit from programmes that increase preparedness to deliver vaccines during pandemics.

WHO recommends HPV DNA testing and triaging as a cervical screening strategy for WLHIV [3]. Due to the suboptimal specificity of the HPV DNA test, triage is essential for WLHIV to distinguish between women who need immediate treatment and those who can be followed up. Although these recommendations were launched towards the end of data collection for our study, a few sites already implemented HPV DNA testing, while maintaining other visual methods for screening and triage. Insufficient infrastructure and financial constraints are obstacles to implementing screen-triage-treat strategies at many facilities, and VIA screening remains common [15, 25, 26]. Visual screening is less resource-intensive and women are likely to be treated the same day they are diagnosed, which increases retention in care [6]. Facilities that wish to transition to HPV DNA testing will have to strengthen their local laboratory infrastructure, improve their quality assurance systems and seek more financing.

Invasive CC management remains challenging in several countries in SSA mostly due to limited infrastructure, limited specialized workforce and unaffordability to women [27]. A recent population-based cohort study in SSA found that only one in six women with CC received cancer-directed treatment

with curative potential and about two-thirds of women never accessed treatment [28]. Across sites, women were often referred for invasive CC management and mainly tracked through phone calls/messaging. Since mobile phones proliferate in SSA counties, it is feasible to text women follow-up reminders [29, 30]. Financial limitations are harder to overcome: earlier studies reported the cost of diagnostic tests, medication and travel as the main financial barriers [31, 32]. At the time of our survey, pre-cancer and CC diagnosis and treatment services were not free in about two-thirds of sites. More funding is needed to ensure women's access to invasive CC diagnosis and treatment methods in SSA to improve outcomes as for women in high-income countries [33].

Routinely collected patient data disaggregated by HIV status were rare at our study sites. Fragmented funding and data systems limit the availability of patient data, making it difficult to improve integrated health programmes [11, 34]. The data available did allow us to see attrition rates varied widely along the steps of CC cascades. For example, attrition rates ranged between 0% (George Health Centre, Zambia) and 86% (Kanyama, Zambia) for women screened positive who should have proceeded to pre-cancer treatment. A previous study in South Africa reported an attrition rate of about 70% between cascade steps [14], but a similar study conducted in Newlands Clinic (Zimbabwe) found attrition rates were less than 20% between cascade steps [16]. Screening and attrition rates at Newlands may be lower because it receives designated funding for CC prevention and invests in human resources to monitor its programme. Keeping the long-term benefits of investing in CC prevention in mind, Governments may consider other innovative ways to sustain finance beyond grants. Quality assurance and monitoring are indispensable for any effective CC prevention programme. For monitoring to be feasible, data systems that collect data for pre-defined indicators in a consistent fashion are crucial. CC prevention facility-based indicators developed specifically for WLHIV [35] should be considered in these settings. Monitoring CC occurrence and outcomes, including incidence and survival, requires population-based cancer registries. Where electronic records exist, record linkage of cancer registries and death registries with HIV and CC screening data may help to fill gaps in HIV status and survival data, respectively [6]. Although almost all sites studied had electronic data systems which have been shown to be more efficient in programme monitoring [36], only half of them collected data on CC prevention and care, and less than half linked these data to population and hospital-based cancer registries. Countries could consider implementing some of the good practices reported in Supplement 13. This could potentially improve efficiency along the screening pathway.

Our study was strengthened by the use of internationally standardized tools to co-develop our survey with country representatives, improving its validity for each context. Focusing on WLHIV allowed us to identify the needs of this underserved population and see gaps across the CC continuum that may have been overlooked in more general studies. Analysing routinely collected data gave us a clearer picture of the situation on the ground at these sites.

We were also faced with some limitations. Since we included only facilities that belong to the IeDEA consortium receiving some research funding, the situation on the ground may be worse than we describe, especially since we restricted the study to sites with more advanced CC prevention programmes. Also, the service delivery and monitoring landscape for CC may have changed since the time of data collection in some sites.

4.1 | Policy implications and conclusion

Facility-based data have contributed significantly to national and global monitoring of HIV. Governments and partners have sought to provide CC prevention and care for WLHIV across SSA and data for monitoring thereof. But insufficient infrastructure and financial challenges hinder these efforts, and impede both monitoring efforts and women's access to HPV vaccination, diagnostic and treatment services as reported across the sites studied. Governments should expand access to treatment infrastructure for cervical pre-cancer, diagnostic and treatment services for invasive CC, and strengthen linkages between these primary healthcare clinics and referral services. Governments should leverage the existing electronic HIV data systems across these sites to strengthen CC data collection and monitoring. Collecting and analysing these essential data will allow these governments and stakeholders to better plan, target, tailor, and scale-up sustainable CC prevention and care interventions and track the nation's progress towards the 2030 CC elimination targets in a standardized fashion.

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COMPETING INTERESTS

The authors declared no competing interests.

AUTHORS' CONTRIBUTIONS

SLA-K, MD, K-GT, AJ, KA, KW-K, PB, MY, SPB, SB, AM, AS, CC and JB conceived the study, wrote the concept and drafted the survey. TD supported data curation and analysis, BM, CT, GM, HT, JM, OE, OO, MJ and K-GT coordinated data collection in all sites. SLA-K and JB wrote the first draft of the manuscript. All co-authors reviewed and approved the final manuscript.

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DISCLAIMER

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

DATA AVAILABILITY STATEMENT

The Supplementary Files contain most of the data that support the findings of our study. Further information is available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional information may be found under the Supporting Information tab for this article:
Supplement Table 1: HPV vaccination
Supplement Table 2: Cervical cancer diagnosis and treatment/management
Supplement Table 3: Laboratory testing and Quality Assurance
Supplement Table 4: Referral and tracking
Supplement Table 5: Facility characteristics associated with the availability of CC data for WLHIV
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Supplement Table 12: List of sites by region and country
Supplement 13: Good practices identified in sites visited

4.4. Publication 4

Breast cancer in women by HIV status: a report from the South African National Cancer Registry

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Own contribution: I led the conceptualization of the study and was responsible for the comprehensive analysis of the data, including the creation of all tables and figures. I wrote the initial draft of the manuscript and the supplementary materials. Additionally, I addressed feedback from co—authors and reviewers throughout the peer-review process. I presented the preliminary results as a poster presentation at the 13th AORTIC International Conference in Africa, which was held online due COVID-19 and at the GHS Annual Symposium in Gerzensee, Switzerland.

PLOS ONE

RESEARCH ARTICLE

Breast cancer in women by HIV status: A report from the South African National Cancer Registry

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Abstract

Background

Breast cancer (BC) is the leading cause of cancer-related morbidity and mortality in women living in South Africa, a country with a high HIV burden. However, characteristics of the double burden of HIV and BC in South Africa have not been properly investigated. We described characteristics of BC cases by HIV status in South Africa.

Methods

In this nationwide South African study, we obtained BC records for women aged ≥15 years diagnosed in the public health sector between January 2004 and December 2014. We included records from the National Cancer Registry that had been linked to HIV-related laboratory records from the National Health Laboratory Service. We assessed the odds of being HIV positive versus HIV negative in relation to patient-, cancer-, and municipality-related characteristics.

Results

From 2004–2014, 40 520 BC cases were diagnosed in women aged ≥15 years. Of these, 73.5% had unknown HIV status, 18.7% were HIV negative, and 7.7% were HIV positive. The median age at BC diagnosis was 43 years (interquartile range [IQR]: 37–52) in HIV positive and 57 years (IQR: 46–68) in HIV negative women, respectively. The odds of being HIV positive was higher for women who were aged 30–34 years compared to women aged 35–39 years at cancer diagnosis (odds ratio [OR] 1.38, 95% confidence interval [CI] 1.10–1.71), Black versus non-Black (OR 6.41, 95% CI 5.68–7.23), diagnosed with cancer in rural versus urban areas (OR 1.59, 95% CI 1.40–1.82) and diagnosed in municipalities with low and

research@nhls.as.za) for researchers who meet the relevant criteria for access to these data. As per NHLS policy and Regulation 380, under no circumstances are we allowed to share any individual/person-level data publicly. Sharing such data would compromise the privacy and confidentiality of the individuals in our data set. We now included this statement as a standalone supplementary file.

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Abbreviations: ART, antiretroviral therapy; CDW, Corporate Data Warehouse; CIs, Confidence Intervals; HIV, Human Immunodeficiency Virus; IARC, The International Agency for Research on Cancer; ICD-O-3, The International Classification of Diseases for Oncology; IQR, Interquartile range; NCR, National Cancer Registry; NHLS, The National Health Laboratory Services; ORs, Odds Ratios; RNA, Ribonucleic Acid; SEP, The Socio-Economic Position; The SAIMD 2011, The South African Multiple Deprivation Index for 2011.

middle (OR 3.46, 95% CI 2.48–4.82) versus high socioeconomic position (OR 2.69, 95% CI 2.11–3.42).

Conclusion

HIV status was unknown for the majority of BC patients. Among those with known HIV status, being HIV positive was associated with a younger age at cancer diagnosis, being Black and receiving care in municipalities of poor socioeconomic position. Future studies should examine opportunities to integrate HIV and BC control programs.

Introduction

Breast cancer is the leading cause of cancer-related morbidity and mortality in women globally [1], and breast cancer incidence rates are rising in Sub-Saharan Africa [2]. The International Agency for Research on Cancer (IARC) estimated that in 2020, breast cancer accounted for 27.3% of all new cancer cases in women in sub-Saharan Africa [3], affecting more than 129 000 women in this region [4]. The rapid increase of breast cancer incidence rates in Sub-Saharan Africa are attributable to exogenous and endogenous factors. The risk factors associated with breast cancer are complex, and include changing population demographics and lifestyle, as well as environmental factors, genetics, and accessibility to screening and diagnostic services [1, 5–7]. Breast cancer is the most frequently diagnosed cancer among women in South Africa as well, accounting for 23% of all female cancers diagnosed in 2019 [8]. The rising burden of breast cancer in women in South Africa coincides with the high prevalence of HIV [3], where almost a quarter of women in their reproductive ages (15–49 years) are HIV positive (23.5%, CI 15.6–31.6) [9]. Over the past decade, governments in the African region, including South Africa, have made great political and economic efforts to fight HIV/AIDS and to increase access to antiretroviral therapy (ART), resulting in a significant increase of the average life expectancy of people living with HIV [4]. As a result, breast cancer cases are expected to be diagnosed more frequently in women living with HIV as well. In addition, existing challenges to timely detect, diagnose, and treat breast cancer patients in the region significantly influence the disease outcome, especially in groups of lower socio-economic position and women living with HIV [10].

In this South African nation-wide study, we described breast cancer cases in women aged 15 years and older diagnosed in public sector laboratories between 2004 and 2014. We evaluated the association between patient's HIV status and age, ethnicity; tumour morphology and year of breast cancer diagnosis; urbanization and socio-economic position based on municipality of the cancer-reporting laboratory.

Methods

Study design and setting

The South African National Cancer Registry (NCR) has been conducting cancer surveillance since 1986 and serves as South Africa's main source of national cancer incidence data. In this case-only study, we used records from the NCR to identify women diagnosed with breast cancer between January 2004 and December 2014. It is a pathology-based cancer registry, and both public and private laboratories are legislated to report all cancer cases to NCR [11]. The NCR is a division of the National Health Laboratory Services (NHLS), the largest diagnostic

pathology service in the country. The NHLS provides laboratory and health services to over 80% of the national population through a network of public sector laboratories in all the nine provinces of South Africa [12]. The NHLS' Corporate Data Warehouse (CDW) is a centralized electronic data repository for all public sector laboratory data, including HIV-related tests and cancer pathology reports.

Study participants

From the South African NCR database, we retrieved all records of women aged 15 years and older (in this manuscript referred as "patients") diagnosed with breast cancer in the public health sector from January 2004 to December 2014. We excluded cancer patient records from the private sector, since the source of HIV-related laboratory data used to determine the HIV status was provided by the NHLS's CDW, which services the public sector only. We assumed that patients diagnosed with HIV in the public sector, would also have received a cancer diagnosis in the public sector, and that patients diagnosed with HIV in the private sector, would have received their cancer diagnosis in the private sector.

Study variables, data source and measurement

We assessed patient-related characteristics: HIV status, age at breast cancer diagnosis, and ethnicity; cancer-related characteristics: tumour morphology and year of cancer diagnosis; and municipality-related characteristics: urbanization, municipality socio-economic position (SEP), and province. HIV status, age at breast cancer diagnosis and ethnicity were extracted from the cancer pathology records. For records where the HIV status was missing, the NCR used probabilistic record linkage methods to match HIV-related laboratory records from the NHLS' CDW to determine HIV status. The HIV-related records included HIV diagnostic tests, CD4 cell counts and percentages, and HIV RNA viral loads from the public sector laboratories. Individuals were assigned HIV positive status if the pathology report indicated HIV positive status, if any HIV diagnostic test was positive or if HIV monitoring tests were recorded. HIV negative status was assigned if the HIV test results were negative. If the HIV result was indeterminate, unavailable or neither positive nor negative, the HIV status was considered unknown [13]. For cancer records where the information of the patient's ethnicity was missing, the NCR used a hot-deck imputation method to impute missing ethnicity [14]. A reference database of approximately 1.4 million surnames with self-reported ethnicity was used to classify patients as Black, White, mixed ancestry and Indian/Asian, and unknown [14]. We used the International Classification of Diseases for Oncology (ICD-O-3) [15] coding system to identify breast cancer cases (topography code C50). We used the name of the cancer-reporting laboratory and determined its location (municipality) and SEP. The municipal SEP was based on the South African Index of Multiple Deprivation (the SAIMD) that was developed using census data [16]. The SAIMD describes multiple deprivation at ward level and combines indices of four domains or dimensions of deprivation (material, employment, education deprivation and living environment deprivation). The higher the SAIMD score, the more deprived the ward. The ward level SAIMD was then used to determine municipal SAIMD scores, by calculating the population weighted average rank of the wards within a municipality [16–18]. Patients were assigned the municipal SAIMD score based on the location of the laboratory that reported their breast cancer diagnosis. We also used the location of the laboratory providing breast cancer diagnosis to determine urbanization using the National Department of Health's data dictionary [19].

Data management

For analyses purposes, we classified age in 5-years age groups, and we combined the first two age groups into one (15–24 years) as the number of breast cancer cases was small. Tumour morphology was categorized based on ICD-O-3 classification (topography code C50) [15] as follows: ductal and lobular neoplasms, epithelial neoplasms, adenocarcinomas, and other morphology types of breast cancer. Ethnicity was defined as per Statistics South Africa groupings in Black, White, Coloured (mixed race), and Asian. However, because of an unequal distribution of case numbers among categories, we combined White, Coloured (mixed race) and Asian in non-Black group for statistical analyses. We categorized the year of breast cancer diagnosis for statistical analyses into the following categories: 2004–2006, 2007–2010, and 2011–2014. We defined the area where the cancer reporting facility was located as urban, rural, and unknown, according to the South African National Department of Health Data Dictionary [19]. We presented the municipality SEP in three categories based on the multiple deprivation rank of the municipality of the cancer reporting facility: low ($\leq$78), middle (78–155) and high ($>$155). Provinces were defined according to the South African Government as Eastern Cape, Free State, Gauteng, KwaZulu-Natal, Limpopo, Mpumalanga, Northern Cape, North West, and Western Cape.

Data analyses

For descriptive analyses, we presented results as frequencies and percentages for categorical variables, and mean and interquartile ranges [IQR] for continuous variables stratified by HIV status (positive, negative, and unknown). We conducted a Wilcoxon rank-sum test to compare median age at cancer diagnosis between patients who were HIV negative and HIV positive, and a chi-squared test to assess differences between patients with known and unknown HIV status; for both tests we set the a significance level at 0.05. In this case only study, we used univariable and multivariable logistic regression models to estimate odds ratios (ORs) with 95% confidence intervals (CIs) of being HIV positive versus HIV negative among breast cancer patients in relation to age at cancer diagnosis, ethnicity (Black and non-Black), year of cancer diagnosis, as well as municipality SEP and urbanization of cancer diagnosing facility. The logistic regression analyses were restricted to breast cancer cases with known HIV status. We conducted a sub-group analysis restricted to Black women diagnosed with breast cancer, as they comprised the majority of our dataset. We assessed interactions between HIV and other factors of interest (age, population group, and calendar period) using likelihood ratio tests at the 5% significance level. We used StataMP 16 (StataCorp Ltd, Texas, US) for all analyses.

Ethical approval

We sought permission to use the routinely collected NHLS and NCR data from the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg, who possess appropriate ethical approvals for the Burden of Cancers Attributable to HIV in South Africa (2004–2014) (The BCAH)(Ethical Clearance Number: M160944) and for the South African HIV Cancer Match (SAM) Study (Protocol Ref No: M190594).

Results

From 2004 to 2014, 664 870 cancer cases were reported to the South African NCR (S1 Fig). We excluded 335 589 records that were reported from the private sector. Of the 41 505 breast cancer cases reported, 978 cases were diagnosed in male patients and 7 cases in patients younger

than 15 years. Finally, we included 40 520 breast cancer cases diagnosed in women aged 15 years and older in our study.

Table 1 presents patient-, cancer- and municipality-related characteristics by HIV status (positive, negative, unknown). The overall median age at breast cancer diagnosis was 55 years (IQR: 45–65 years). Ductal and lobular neoplasms were the most common morphology types, accounting for 85.2% of breast cancer cases. Most (60.1%) breast cancer patients were Black, 19.7% were White, 16.4% were Coloured, and 3.8% were Asian. Overall, most breast cancer cases were reported by laboratories located in urban areas (71.3%), in municipalities with high SEP (85.4%), and by public laboratories located in Gauteng (32.1%) and Western Cape provinces (26.2%).

Of all breast cancer patients, 7.7% were HIV positive, 18.7% were HIV negative, and in 73.5% the HIV status was unknown (Table 1). We found statistically significant differences in all patient-, cancer-, and municipality-related characteristics when comparing patients with known and unknown HIV status (S1 Table). The percentage of breast cancer patients with known HIV status (both HIV positive and negative) increased from 5.9% in 2004 to 39.4% in 2014. Among patients with known HIV status, the percentage of HIV positive declined from 38.0% in 2004 to 27.2% in 2014. Fig 1 shows median age at breast cancer diagnosis by HIV status and year of cancer diagnosis. The median age (IQR) was 43 years (37–52) for HIV positive, 54 years (45–64) for HIV negative and 57 years (46–68) for breast cancer patients with unknown HIV status. The difference in median of age at diagnosis between HIV positive and HIV negative breast cancer patients was statistically significant ($p < 0.001$) throughout the whole study period. Fifty-eight percent of the HIV positive breast cancer patients, but only 26.5% of the HIV negative and 23.3% of the HIV unknown, were younger than 45 years at the time of their breast cancer diagnosis. There were marked ethnic differences by HIV status with the percentage of women of Black ethnicity being much higher among HIV positive (86.2%) than among HIV negative patients (44.1%); the opposite was true for all the other ethnic groups. Tumour morphology did not vary by HIV status, with the large majority (85.2%) having a ductal or lobular morphology regardless of their HIV status. Most breast cancer patients were diagnosed in facilities that were located in an urban area (HIV positive 70.4%, HIV negative 82.9%, HIV status unknown 68.0%) and in municipalities with high SEP (HIV positive 84.6%, HIV negative 97.2%, HIV status unknown 82.1%). Forty-three percent of all HIV positive cases were diagnosed in laboratories located in Gauteng province, and 49.4% of all HIV negative cases were diagnosed in Western Cape Province.

The percentage of breast cancer cases by age and HIV status differed between Black and non-Black patients. In breast cancer patients with known HIV status (Fig 2), there were more HIV positive than HIV negative cases in each age group younger than 45 years in Black patients. In non-Black patients, there were more HIV negative than HIV positive breast cancer patients in each age category. The highest percentage of both Black and non-Black breast cancer patients were diagnosed in laboratories located in municipalities with high SEP (Table 1). Among breast cancer patients with known HIV status (Fig 3), a higher percentage of HIV positive patients were diagnosed in laboratories located in municipalities with low and middle SEP compared to HIV negative patients. This was more prominent among Black patients.

Results from univariable and multivariable logistic regressions were similar, see S2 Table. In the complete-case multivariable logistic regression model (Fig 4), patients who were diagnosed with breast cancer at ages 30–34 years were more likely to be HIV positive compared to women aged 35–39 years (OR 1.38, 95% CI 1.10–1.71). The odds of being HIV positive decreased progressively for ages above 39 years. The odds of being HIV positive was about six times (OR 6.41, 95% CI 5.68–7.23) higher among Black breast cancer patients compared to non-Black women. Breast cancer patients who were diagnosed in laboratories located in rural

Table 1. Characteristics of female breast cancer patients (n = 40 520) stratified by HIV status.

	HIV positive N (%)	HIV negative N (%)	HIV unknown N (%)	Total
PATIENT-RELATED CHARACTERISTICS				
Age at cancer diagnosis [years]				
15–24	27 (0.9)	29 (0.4)	131 (0.4)	187 (0.5)
25–29	127 (4.1)	114 (1.5)	422 (1.5)	663 (1.7)
30–34	381 (12.2)	280 (3.7)	1 004 (3.5)	1 665 (4.2)
35–39	544 (17.5)	563 (7.5)	1 793 (6.2)	2 900 (7.3)
40–44	591 (19.0)	822 (10.9)	2 772 (9.5)	4 185 (10.5)
45–49	499 (16.0)	1 029 (13.6)	3 380 (11.6)	4 908 (12.4)
50–54	374 (12.0)	1 079 (14.3)	3 460 (11.9)	4 913 (12.4)
55–59	258 (8.3)	988 (13.1)	3 486 (12)	4 732 (11.9)
60+	311 (10.0)	2 650 (35.1)	12 618 (43.4)	15 579 (39.2)
Missing	23 (n.a.)	37 (n.a.)	728 (n.a.)	788 (n.a.)
Median age (IQR)	43 (37–52)	54 (45–64)	57 (46–68)	55 (45–66)
Ethnicity				
Asian	29 (0.9)	187 (2.5)	1 277 (4.5)	1 493 (3.8)
Black	2 625 (86.2)	32 54 (44.1)	17 526 (61.4)	23 405 (60.1)
Colored	217 (7.1)	1 995 (27)	4 177 (14.6)	6 389 (16.4)
White	174 (5.7)	1 941 (26.3)	5 554 (19.5)	7 669 (19.7)
Missing	90 (n.a.)	214 (n.a.)	1 260 (n.a.)	1 564 (n.a.)
CANCER-RELATED CHARACTERISTICS				
Tumour morphology				
Ductal and Lobular Neoplasms	2 695 (86)	6 521 (85.9)	25 294 (84.9)	34 510 (85.2)
Epithelial Neoplasms, NOS	208 (6.6)	530 (6.7)	2 079 (6.7)	2 817 (6.9)
Adenocarcinomas	78 (2.5)	213 (2.8)	860 (2.9)	1 151 (2.8)
Others	154 (4.9)	327 (4.3)	1 561 (5.2)	2 042 (5.0)
Year at cancer diagnosis				
2004	70 (2.2)	114 (1.5)	2 915 (9.8)	3 099 (7.6)
2005	134 (4.3)	370 (4.9)	2 794 (9.4)	3 298 (8.1)
2006	167 (5.3)	450 (5.9)	2 872 (9.6)	3 489 (8.6)
2007	200 (6.4)	483 (6.4)	2 829 (9.5)	3 512 (8.7)
2008	282 (9.0)	575 (7.6)	2 886 (9.7)	3 743 (9.2)
2009	304 (9.7)	726 (9.6)	2 819 (9.5)	3 849 (9.5)
2010	354 (11.3)	763 (10.1)	2 827 (9.5)	3 944 (9.7)
2011	410 (13.1)	9 91 (13.1)	2 588 (8.7)	3 989 (9.8)
2012	452 (14.4)	1 076 (14.2)	2 776 (9.3)	4 304 (10.6)
2013	398 (12.7)	1 068 (14.1)	2 432 (8.2)	3 898 (9.6)
2014	364 (11.6)	975 (12.8)	2 056 (6.9)	3 395 (8.4)
MUNICIPALITY- RELATED CHARACTERISTICS				
Urbanization				
Rural	895 (29.6)	1 298 (17.1)	8 283 (32.0)	10 476 (28.7)
Urban	2 133 (70.4)	6 289 (82.9)	17 606 (68.0)	26 028 (71.3)
Missing	107 (n.a.)	4 (n.a.)	3 905 (n.a.)	4 016 (n.a.)
Socio-economic position				
Low	176 (5.8)	68 (0.9)	1 934 (7.5)	2 178 (6.0)
Middle	290 (9.6)	148 (2)	2 695 (10.4)	3 133 (8.6)
High	2 562 (84.6)	7 370 (97.2)	21 182 (82.1)	31 114 (85.4)

(*Continued*)

Table 1. (Continued)

	HIV positive N (%)	HIV negative N (%)	HIV unknown N (%)	Total
Missing	107 (n.a.)	5 (n.a.)	3 983 (n.a.)	4 095 (n.a.)
Province				
Gauteng	1 303 (43.0)	1 943 (25.6)	8 429 (32.7)	11 675 (32.1)
Western Cape	428 (14.1)	3 748 (49.4)	5 384 (20.9)	9 560 (26.2)
Eastern Cape	247 (8.2)	605 (8)	3 786 (14.7)	4 638 (12.7)
Free State	323 (10.7)	590 (7.8)	1 760 (6.8)	2 673 (7.3)
Limpopo	258 (8.5)	77 (1.0)	2 197 (8.5)	2 532 (7.0)
North West	216 (7.1)	290 (3.8)	1 415 (5.5)	1 921 (5.3)
Mpumalanga	149 (4.9)	62 (0.8)	1 229 (4.8)	1 440 (4.0)
Northern Cape	60 (2.0)	124 (1.6)	916 (3.6)	1 100 (3.0)
Kwazulu-Natal	44 (1.5)	148 (2.0)	695 (2.7)	887 (2.4)
Missing	107 (n.a.)	4 (n.a.)	3 983 (n.a.)	4 094 (n.a.)
Total	**3 135 (7.7)**	**7 591 (18.7)**	**29 794 (73.5)**	**40 520**

% = column percentages among women with no missing data, IQR = Interquartile range, n.a.–not applicable

https://doi.org/10.1371/journal.pone.0305274.t001

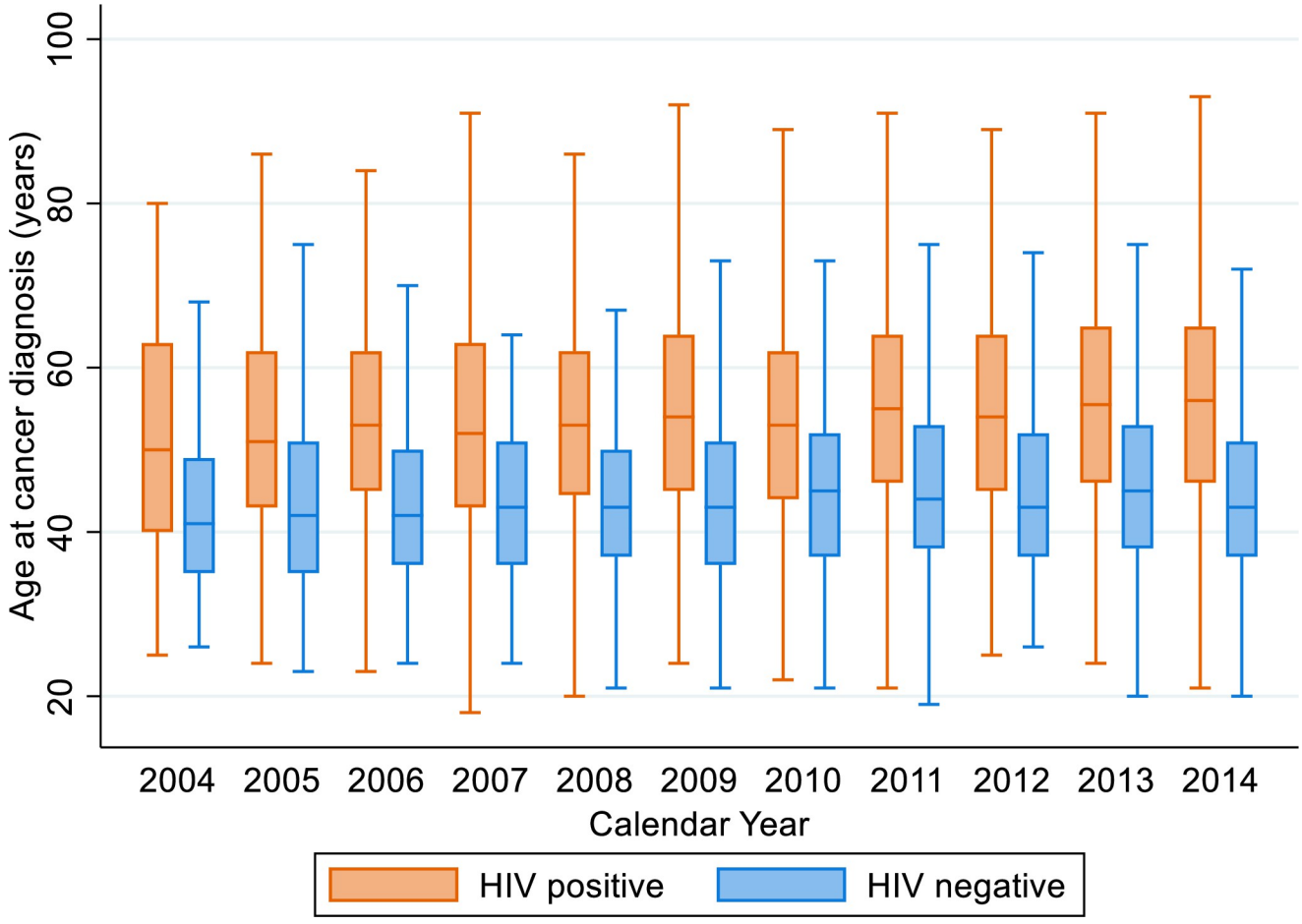

Fig 1. Median age at breast cancer diagnosis by HIV status and by year of cancer diagnosis.

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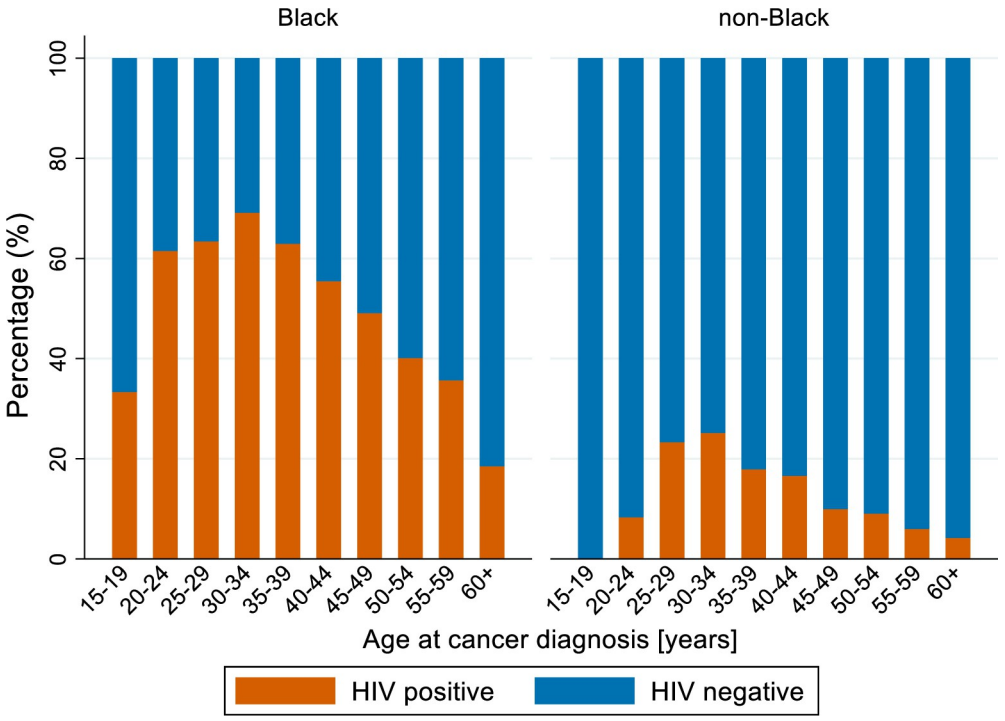

Fig 2. The percentage of black and non-black breast cancer patients with known HIV status by age at cancer diagnosis and HIV status (HIV positive and HIV negative).

https://doi.org/10.1371/journal.pone.0305274.g002

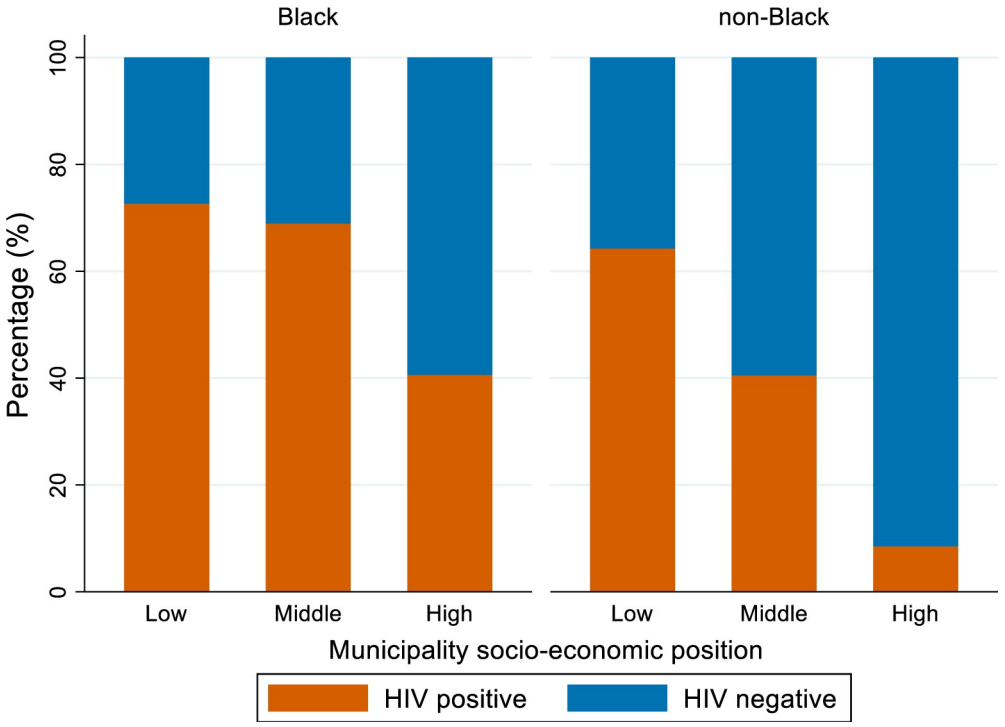

Fig 3. The percentage of black and non-black breast cancer patients with known HIV status by municipality socio-economic position (SEP) and HIV status (HIV positive and HIV negative).

https://doi.org/10.1371/journal.pone.0305274.g003

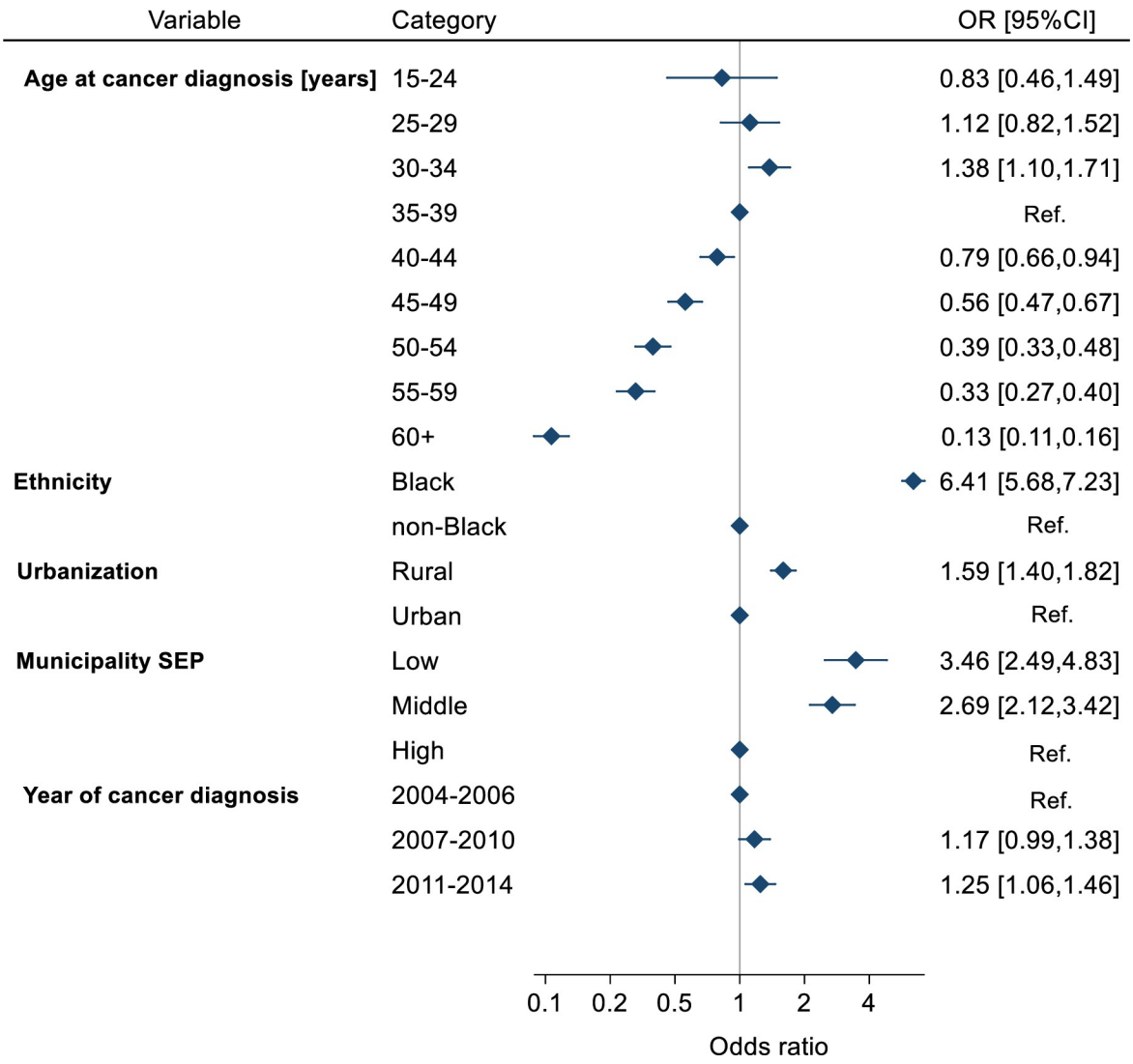

Fig 4. Multivariable logistic regression: Factors associated with being HIV positive in breast cancer female patients. Factors included in the model: age at cancer diagnosis, ethnicity, year of cancer diagnosis, municipality socio-economic position (SEP) and urbanization. CI–confidence interval; OR–odds ratio; Ref.–reference category.

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areas were 1.6 times more likely to be HIV positive compared to breast cancer patients who were diagnosed in laboratories located in urban areas (OR 1.59, 95% CI 1.40–1.82). Patients whose breast cancer was diagnosed in public laboratories located in municipalities with low and middle SEP were more likely to be HIV positive compared to patients diagnosed in municipalities with high SEP (OR 3.46, 95% CI 2.48–4.82 and OR 2.69, 95% CI 2.11–3.42, respectively). The odds of being HIV positive increased gradually over time, being highest among patients who were diagnosed with breast cancer in the most recent study years, i.e., 2011–2014 (OR 1.25, 95% CI 1.06–1.46). In a sub-group analysis restricted to Black women, our findings were confirmed (S3 Table).

Discussion

In this South-African nation-wide study, we evaluated 40 520 breast cancer cases in women aged 15 years and older, diagnosed in a public health sector laboratory between 2004 and 2014.

Our study has shown that the median age at breast cancer diagnosis was 10 years lower in breast cancer patients who were HIV positive as compared to breast cancer patients who were HIV negative. Black breast cancer patients were almost seven times more likely to be diagnosed with HIV compared to non-Black breast cancer patients.

Our study had several limitations. The South African NCR is a pathology-based registry, and cancer cases that are diagnosed radiologically and clinically only are not captured. This may lead to underreporting of breast cancer cases. We lacked clinical (i.e., stage and receptor status of breast cancer at diagnosis) and patient information that is associated with the development of breast cancer, such as tobacco use, alcohol consumption, overweight and obesity, lack of physical activity, older age at first birth, low fertility, or family history. In our study population, HIV status was unknown for most patients. A high percentage of missing data for HIV status potentially introduced selection bias and limited the generalizability of our findings. We could not compare the risk of developing breast cancer in HIV positive versus HIV negative women, as our dataset included breast cancer cases only. To describe municipality SEP, we used small area level estimates of deprivation generated from national consensus ward-level data [16–18]. This approach assumed a uniform level of deprivation areas across the municipality, which not necessarily reflect the actual distribution of deprivation. While it is designed to provide highly accurate estimates, there is a risk of ecological bias if not interpreted correctly.

The relationship between HIV and breast cancer in women is not fully understood [20]. While one review from South Africa found an increased risk of breast cancer in HIV positive women [21], other African studies did either not find evidence for an association [22–24], or they found a positive association between HIV and breast cancer [25]. In our study, 29.2% of breast cancer patients with a known HIV status were HIV positive. South African hospital-based studies of women diagnosed with breast cancer conducted between 2006 and 2014, reported that 18–20% patients were HIV positive [22, 26, 27]. Another prospective study that was examining women newly diagnosed with breast cancer in six public hospitals in South Africa, reported that 22% of breast cancer patients were HIV positive [28]. While the prevalence of HIV positive breast cancer patients in our cohort seems high, it is important to note that in cases where HIV status was missing, text mining of pathology reports was used to obtain HIV status. Doctors are more likely to note down the HIV status of an HIV positive patient increasing the likelihood of picking up those that were tested positive compared to those that tested negative or never tested.

The median age at breast cancer diagnosis in our study (55 years) was similar to that reported in previous studies that included women from several African countries, including South Africa [27, 29–33]. In Sub-Saharan Africa, patients with breast cancer generally present at a relatively early age regardless of HIV status [20, 34]. The different age distributions of the underlying population can mainly explain the apparently early onset breast cancer in African women [34, 35]. In African countries, the population structure is skewed towards younger age groups, and the number of new breast cancer cases are expected to be higher where the female population is larger. Therefore, lower median age at breast cancer diagnosis does not necessarily mean that younger women are more likely to have breast cancer [34, 35]. Likewise, in our study HIV positive patients were diagnosed with breast cancer on average 10 years earlier than HIV negative patients were. This is in line with previous studies evaluating HIV positive breast cancer patients in South Africa [22, 27, 28, 32, 33, 36]. The age difference at breast cancer diagnosis between HIV positive and HIV negative patients has been discussed in previous studies. As the HIV positive population is on average younger than the HIV negative population [37] this will likely explain the apparent differences and may not carry an etiological significance.

Among breast cancer patients with known HIV status, the HIV prevalence in Black patients was 44.6% as compared to less than 10% in non-Black patients. Other studies that assessed

HIV status in South African breast cancer patients also have found that HIV prevalence in Black breast cancer patients was higher compared to the HIV prevalence in non-Black patients; and it ranged from 18.4% to 33.7% [22, 26–28, 36, 38–40]. We assumed that in our study based on routine care data, healthcare providers might have offered HIV tests more often to Black patients than to non-Black patients, as Black people in South Africa are at higher risk for contracting HIV as compared to non-Black people [41]. Nevertheless, the reasons for the higher HIV prevalence in Black breast cancer patients in our study, in comparison to other studies, remain unclear. The percentage of breast cancer patients with unknown HIV decreased from 94.1% in 2004 to 60.6% in 2014. This might reflect improving HIV testing services availability in South Africa across the study period and is in line with previous studies in South Africa [22]. Still, many women diagnosed with breast cancer were unaware of their HIV status by the end of our study period, especially in women aged older than 50 years. This is supported by an earlier study on HIV testing patterns in South Africa, that found that older cancer patients were less likely to be tested for HIV than younger patients [39]. They also reported that 14.3% HIV positive patients diagnosed with breast cancer were unaware of their HIV status.

In our study, most patients, regardless of HIV status, were diagnosed with breast cancer in laboratories located in urban municipalities or in municipalities with high SEP. Our measures of SEP and urbanization describe the municipality where the breast cancer diagnosis laboratory is located, it does not describe a woman's residential or her individual socio-economic circumstances. Nevertheless, it is well-established that area socio-economic factors affect the risk of developing breast cancer as well as the likelihood of the disease being diagnosed at an early stage and properly managed. A recent IARC study [42] found that incidence rates of breast cancer are increasing with increasing levels of socioeconomic development. This can be explained by the higher exposure to relevant risk factors, such as tobacco use, alcohol consumption, overweight and obesity, lack of physical activity, low fertility, and older age at first birth, shorter duration of breastfeeding and later age at menopause, as countries are progressing from low to very high socioeconomic development. A South African study of breast cancer in black woman found that higher household socioeconomic status reduced the odds of having advanced-stage breast cancer at diagnosis [31]. Another South African study explored female specific cancers and their risk factors in women living with HIV and reported that diagnosis of breast cancer was strongly associated with municipalities with high SEP [43]. South African women who were relatively wealthier, better educated [38], with higher socioeconomic status [31], or who are living close to health facility or hospital [26] were more likely to be diagnosed with breast cancer earlier. Hence, women from communities with low SEP and in rural areas are likely to have delayed breast cancer diagnosis. We also found that breast cancer patients diagnosed in laboratories in rural municipalities with low or middle SEP are more likely to be diagnosed with HIV compared to their counterparts. In South Africa, socioeconomic factors such as unstable housing and lower education level impact the odds of HIV infection [44].

Future research should aim to properly address and quantify the anticipated increasing numbers of women with breast cancer and HIV in South Africa as well as in other African settings with a high HIV prevalence. More research is needed to understand HIV testing practices in healthcare facilities, and breast cancer patients should be offered HIV testing if they do not know their status. Integrating breast cancer detection programs into existing health services, e.g., HIV/AIDS clinics should be considered, but with caution to not overload existing infrastructure and workforce. In the resource-limited settings, down staging of the disease may be achieved by improving awareness among women, communities, and health professionals [32, 45, 46], in addition to supporting early detection and improving timely access to appropriate treatment [47]. Addressing structural, sociocultural, personal and financial barriers to early

presentation and diagnosis, and sustainable community and healthcare worker education may reduce breast cancer morbidity and mortality [30, 47–49]. Although the association between HIV and breast cancer is still unclear, it is evident that HIV low socio-economic circumstances are associated with poor survival from breast cancer [20, 32, 36, 37, 50]. Novel approaches to manage and treat multiple comorbidities in African women are needed. To quantify the double burden from breast cancer and HIV infection, high quality population-based data are essential. Improvements in cancer data collection and linkage of clinical and mortality data to existing cancer surveillance programs are urgently needed. In addition, socioeconomic data on individual level, as opposed to area-based level, can enhance insights into the social and economic impact on the risk of developing of breast cancer and on its outcomes. By exploring both perspectives, we can achieve a more comprehensive understanding of these factors.

Conclusion

Our study provides insights on breast cancer cases stratified by HIV status and contributes to better understand the double burden from HIV and breast cancer in South Africa. With the ageing of the population living with HIV, we can expect a growing burden of breast cancer in this population, which may have a significant impact on the health and quality of life of women living with HIV. Integrating breast cancer prevention and diagnostic services in well-established HIV clinics may be a first step toward addressing global disparities in access to, and availability of, breast cancer detection. In South Africa, as well as in other countries with high HIV burden, newly diagnosed breast cancer patients who are unaware of their HIV status should be offered HIV testing to ensure patients are properly managed.

Supporting information

S1 Fig. Flow chart of study cases selection.
(PDF)

S1 File. Minimum data set.
(XLSX)

S1 Table. Characteristics of female breast cancer patients (n = 40 520) stratified by HIV status (known, unknown).
(PDF)

S2 Table. Univariable and multivariable analysis for different explanatory variables in HIV positive breast cancer patients compared to HIV negative breast cancer patients.
(PDF)

S3 Table. Sub-group analysis–univariable and multivariable analysis for different explanatory variables in HIV positive black breast cancer patients compared to HIV negative black breast cancer patients.
(PDF)

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Overall discussion

“Nothing in life is to be feared, it is only to be understood now is the time to understand more, so that we may fear less.” – Marie Curie

5. OVERALL DISCUSSION

In this chapter, I discuss the main findings of the four published publications, presented in the previous chapter. First, I explore the evidence generated by the publications in relation to their specific aims and the overarching aim of this thesis. Afterward, I discuss the methodological aspects, strengths, and limitations of both this thesis and the original publications presented. Following that, I delve into the implications of the findings and their contributions to the real world across various settings. Additionally, I offer an outlook and suggestions for future research, highlighting areas where further investigation could yield significant insights in the cancer prevention and care for women living with HIV in sub-Saharan Africa. Overall, this thesis explores various aspects of the cancer prevention and care continuum, focusing on cervical prevention and care services offered to girls and women living with HIV in sub-Saharan Africa and on breast cancer characteristics in women living with and without HIV in South Africa. All publications within this thesis utilized different study designs and addressed various gaps and challenges in cancer prevention and care among women living with HIV in sub-Saharan Africa.

Section I discusses research efforts aimed at supporting cervical cancer elimination, in girls and women living with HIV in sub Saharan Africa. It presents the development of a tailored monitoring framework through a consensus process with stakeholders (**Publication 1**), summarizes the existing service capacities, efforts, and performance tools, informed by a review of cancer policies (**Publication 2**), and explores cervical cancer prevention and care services offered at HIV clinics, as well as services' utilization, as informed by a facility-based survey (**Publication 3**). This section presents aggregated findings across the cervical cancer prevention and care continuum and emphasizes some qualitative findings gained from discussions with stakeholders. **Section II** critically examines the findings on breast cancer in women living without and with HIV who were diagnosed in South African public sector from 2004 to 2014 (**Publication 4**). It integrates these new epidemiological insights into the broader scientific context, highlighting how the study advances understanding on breast cancer in women living with HIV in sub-Saharan Africa.

For more granular findings on all **Publications 1 – 4**, please refer to the corresponding sections in Chapter 4: RESULTS AND ORIGINAL PUBLICATIONS.

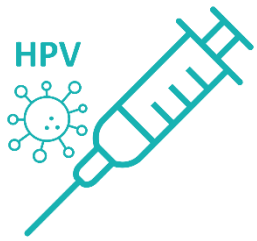
5.1. Section I: Summary of principal findings from Publications 1, 2, and 3

In **Publication 1** (please see Chapter 4.1), I presented the Cervical Cancer Prevention and Care (CCPC) Cascade for women living with HIV in sub-Saharan Africa. The CCPC Cascade outlines domains, indicators, and data variables needed to inform indicators across the cervical cancer prevention and care continuum for women living with HIV. It was developed through a three-round Delphi consensus process with 72 stakeholders working in 15 countries in sub-Saharan Africa. Stakeholders initially revised indicators extracted and selected from a literature review (Round 1), rated them according to five criteria (Rounds 2 and 3), and ranked their importance within each domain across the cervical cancer prevention and care continuum (Round 3). Experts achieved a high-level of agreement (>70% of participants) on five core indicators (high-level agreement on all five criteria) and 12 optional indicators (high-level of agreement on 3 or 4 criteria). In **Publication 2** (please see Chapter 4.2), I participated in reviewing 33 national policies, plans, guidelines, and strategies for cervical cancer control in the nine sub-Saharan African countries with the highest HIV prevalence (HIV prevalence of 10% and above in 2018). All the selected countries had a cancer control policy that included aspects of cervical cancer prevention and care. However, recommendations for cervical cancer prevention and care for women living with HIV differed among countries. In **Publication 3** (please see Chapter 4.3), I presented the results from a facility-based survey conducted at 30 sites across 14 countries in sub-Saharan Africa. The respondents were primarily data or program managers (30% and 27%, respectively) and healthcare professionals (30%). The majority of the surveyed sites were public sector facilities (73%) and located in urban areas (83%). Most of the sites integrated cervical cancer control services on-site (90%, within HIV clinic using existing staff or in another unit in the hospital where the HIV clinic is located) and offered a 'screen and treat' approach (77%). We collected and presented both site-level and aggregated patient-level data.

In the following paragraphs, I summarize and unite the key findings from **Publications 1, 2, and 3** across the cervical cancer prevention and care continuum, highlighting recommendations specifically tailored to girls and women living with HIV when applicable. Further details on these findings are available in the Chapter 4: RESULTS AND ORIGINAL PUBLICATIONS.

Results across the cervical cancer prevention and care continuum

Primary prevention – with focus on HPV prevention



In the policies we reviewed (**Publication 2**), the most commonly reported age group for HPV vaccination was from nine to 13 years. No policy included boys as a target population for HPV vaccination. Mostly a three-dose schedule for HPV vaccination was recommended over a two-dose schedule for the general population of girls. Recommendations for girls living with HIV were rarely defined in the reviewed policies - only Namibia's and Malawi's national cancer policies provided specific considerations for HPV vaccination in individuals living with HIV. HPV vaccination was mostly offered in schools but also being integrated, or there were plans to integrate it, into the national vaccination program. All policies we reviewed recommended sex education, promotion of condom use for sexually active individuals, and warnings against tobacco use. All countries highlighted the need to develop or revise materials for cancer prevention. The facility-based survey (**Publication 3**) revealed that more than half of surveyed sites offered HPV vaccination either currently (33%) or in the past (23%), and in all sites, services were provided at no costs. The majority of sites offering HPV vaccination at the time of the survey targeted only girls under 15 years of age. Only one site offered the HPV vaccine to boys as well. The reported reasons of discontinuing HPV vaccination services included lack of funding (43%), COVID-19 and low community acceptance (14%), completion of pilot/research studies (14%), and services being organized sporadically (29%). At the time of the survey, among the ten sites providing HPV vaccination, only two were able to report HPV vaccination rates for girls living with HIV who were eligible for vaccination at their facilities. In the Delphi process (**Publication 1**), out of the 17 indicators that reached consensus in Round 3, two belong to primary prevention – specifically, HPV prevention. One of the major concerns raised during stakeholders' discussions was the feasibility of collecting the data needed to inform these indicators. Many participants noted that it is often unknown whether a girl or woman has received the HPV vaccine, and in the majority of cases, this information is not available or relies on self-reported sources. Some agreed that these indicators would be very useful when countries adopt HPV vaccination and HPV testing as primary screening method, but some were concerned that such a transition would take years.

Secondary prevention – cervical screening and treatment of pre-cancer lesions

The review of policies (**Publication 2**) found that recommended age to start cervical screening varied across the countries' policies. VIA and Pap smear testing were the most commonly recommended screening methods in the policies we evaluated, but the Pap test was not available in all countries. Histopathology, cryotherapy, and LEEP were the most recommended methods for treating cervical pre-cancer lesions, with all countries reporting the availability of cryotherapy and LEEP. Cervical screening services were mostly integrated into other healthcare units and were not always free of charge. Most countries recommended cervical screening for women living with HIV, with the recommended age to start varying across countries and differing from that of the general population. Only a few countries recommended HPV DNA testing and reported having histopathology as part of their diagnostic services. The recommended screening interval for women living with HIV who tested negative ranged from one to three years, depending on the country. Cervical screening services were either already integrated, or integration into HIV clinics was recommended. The facility-based survey (**Publication 3**) revealed that cervical screening services were typically integrated into routine care at the HIV clinics (67%), provided by either an individual or a team specifically dedicated to the screening activities (83%). Almost one-third of the sites had an invitation system for the eligible population and prioritized women living with HIV. Cervical screening services were predominately provided on-site. Referral for cervical screening was common across sites, though often inconsistent, with only 23% of sites consistently referring women for cervical screening. The VIA was the most frequently used screening method (83%), while HPV DNA testing and triage were performed at less than half of the surveyed sites (40%). Cervical pre-cancer diagnosis commonly involved colposcopy (30%) and histopathology (37%), typically conducted off-side. Cryotherapy (63%), thermocoagulation (43%), and LEEP (57%) were the most common cervical pre-cancer treatment methods. Screen-negative women and women treated for cervical pre-cancer were mostly followed-up every 12 months. The proportions of cervical screening in women living with HIV varied widely, ranging from 4% to 78% across different sites and regions. Similarly, the proportions for cervical pre-cancer treatment in women living with HIV varied, ranging from 14% to 100%. Among the surveyed sites, indicators disaggregated by HIV status were reported by

11 out of 15 sites that reported collecting data on cervical screening, and by two out of ten sites that reported collecting data for cervical pre-cancer treatment.

Most of the 17 indicators that reached consensus in the Delphi process (**Publication 1**) referred to the secondary portion of the cervical cancer prevention and care continuum. Specifically, six indicators were related to screening, three to triage, and two to the cervical pre-cancer treatment outcomes. Among five indicators that achieved a high level of agreement across all five criteria (core indicators), all belonged to the secondary prevention: four focused on cervical screening efforts, and one on the cervical pre-cancer treatment. The consensus on these indicators reflects broader trends noted in other publications within this thesis, highlighting prevalent cervical screening and pre-cancer treatment practices offered at the ART sites.

During discussions along the Delphi process (**Publication 1**), stakeholders voiced several important concerns. They agreed that substantial efforts may be needed to establish and maintain comprehensive documentation of cervical cancer screening at HIV clinics. The reliability and accuracy of such data will depend greatly whether the site uses electronic or paper-based data collection methods. Triage indicators, in particular, drew considerable attention, especially as WHO released the updated recommendations on cervical cancer screening and treatment for women living with HIV during the Delphi process, advising on implementing an appropriate triaging strategy for women living with HIV. This contributed to increased agreement and reaching consensus on triage indicators in later rounds, though they still rated these indicators lowest in terms of feasibility. Stakeholders attributed this low feasibility to the considerable variability in providing triage services and noted that referring women for triage outside their primary screening facilities could result in loss to follow-up. The referral poses additional challenges, as if woman is referred for further diagnosis or treatment off-site, the information of attendance may be missing or rely on patient self-reporting. This situation is further complicated when women, believing they have received adequate treatment, do not prioritize follow-up visits, impacting their continued care and monitoring.

Tertiary prevention: diagnosis and management of invasive cervical cancer

The policy review (**Publication 2**) revealed that the services available for treating invasive cervical cancer included surgery, radiotherapy, and chemotherapy. Recommendations for treating invasive cancer in women living with HIV were rare in the policies reviewed. We evaluated the monitoring practices and found that while monitoring data systems in included countries were widely available, indicators disaggregated by HIV status for monitoring purposes were generally lacking. Through the facility-based survey (**Publication 3**), we discovered that approximately two-thirds of the surveyed sites offered services for the diagnosis (73%) and treatment (67%) of invasive cervical cancer. The most frequently used diagnostic tool was histopathology (40%), although many sites reported that no diagnostic tool was available (27%). Treatment methods included simple and radical hysterectomy, chemotherapy, and radiation therapy, often used in combination at various sites. Only two sites reported patient-level data, indicating that data on treatment for invasive cervical cancer among women living with HIV was rarely collected. Of the 17 indicators that reached consensus in Delphi process (**Publication 1**), two referred to the tertiary portion of the cancer prevention and care continuum: the rate of suspected cervical cancer cases and confirmed cervical cancers. Stakeholders emphasized that diagnosing suspicious cervical cancer cases is subjective and often relies on the healthcare provider's experience. Without a confirmed histological diagnosis, accurately assessing the number of cervical cancer cases at HIV clinics, whether offering cervical cancer prevention and care services on-site or off-site, becomes challenging. This raises justified concerns about the reliability of such data. Nevertheless, it remains important to document these cases at ART sites, ensuring that women are referred for diagnostic services and receive the appropriate treatment.

Other relevant aspects of the cervical cancer prevention and care continuum

This thesis investigated the monitoring, surveillance mechanisms, and costs associated with cervical cancer prevention and care services, informed either by the review of the policies (**Publication 2**) or the facility-based survey (**Publication 3**). The policy review revealed that monitoring and surveillance mechanisms varied, with either paper-based data systems or a combination of electronic and paper-based systems. While all reviewed policies outlined indicators for cervical cancer control programs, with most aligning with WHO recommended global indicators, only four countries provided data disaggregated by HIV status for these indicators. Cervical cancer data registration was prevalent in many countries, though it was mostly present in major cities and not population-wide. The survey found that all sites had data information systems, with 90% being electronic. Of the sites offering HPV vaccination, 70% collected relevant data. Half of the sites collected some data on cervical screening, and several incorporated at least one WHO global monitoring indicator. Less than half sites included HIV status as part of the monitoring indicators.

When examining the costs reported in the reviewed policies, it was revealed that the costs of services were not always explicitly mentioned. In some countries, HPV vaccination was provided free of charge in government healthcare facilities or schools. The costs of cervical screening and diagnostic services were generally free, or offered at no cost to vulnerable groups. However, the costs for treating cervical pre-cancer lesions or invasive cervical cancer varied –some countries offered these services for free in public facilities, while in others, they were unaffordable. According to the facility-based survey, although many sites received financial support from non-governmental organizations (83%), only a portion of this support was allocated to cervical cancer prevention and care activities. At half of the sites, clients were responsible for either the full cost or a portion of the cost for the diagnosis and treatment of cervical disease.

5.2. Section II: Summary of principal findings from Publication 4

Publication 4 (please see Chapter 0) reveals significant insights into the intersection of HIV status and breast cancer in South Africa, one of the countries with the highest HIV prevalence globally. I evaluated 40 520 breast cancer cases in women aged 15 years and older diagnosed with breast cancer in a public health sector laboratory between 2004 and 2014 in South Africa. I presented patient-related characteristics such as age, ethnicity, and median age; cancer-related characteristics including tumor morphology and year of cancer diagnosis; and municipality-related characteristics like urbanization and socio-economic position stratified by women's HIV status. The median age at breast cancer diagnosis was 10 years lower in patients living with HIV compared to those without HIV (Figure 12). Breast cancer patients of Black ethnicity were disproportionately affected by HIV compared to patients of other ethnicities, mirroring the broader HIV epidemic in South Africa. The discrepancy in median age at diagnosis aligns with observed trends in the region, and can be explained by the generally younger age distribution within the population living with HIV.

The odds of being HIV positive in women diagnosed with breast cancer decreased progressively for ages above 39 years. Black women were six times more likely to be diagnosed with HIV compared to non-Black women (OR 6.41, 95% CI 5.68-7.23). Breast cancer patients diagnosed in rural laboratories had 1.6 times higher odds of being HIV positive compared to those diagnosed in laboratories in urban areas (OR 1.59, 95% CI 1.40-1.82). Patients diagnosed with breast cancer in low and middle SEP municipalities were more likely to be HIV positive compared to those diagnosed in high SEP municipalities (OR 3.46, 95% CI 2.48-4.82 and OR 2.69, 95% CI 2.11-3.42, respectively). These findings underscore the importance of ethnic, socioeconomic, and municipal factors in determining HIV status among women diagnosed with breast cancer. Over the study period, there was a substantial improvement in the recording of HIV status, with known statuses rising from 5.9% to 39.4% (

Figure 12). The odds of being HIV positive increased over time, with the highest odds observed in breast cancer patients diagnosed in the most recent years of the study, i.e., 2011-2014 (OR 1.25, 95% CI 1.06-1.46, referent: 2004-2006). These findings most likely reflect the improved access to HIV diagnosis and increased awareness and testing for HIV in South Africa.

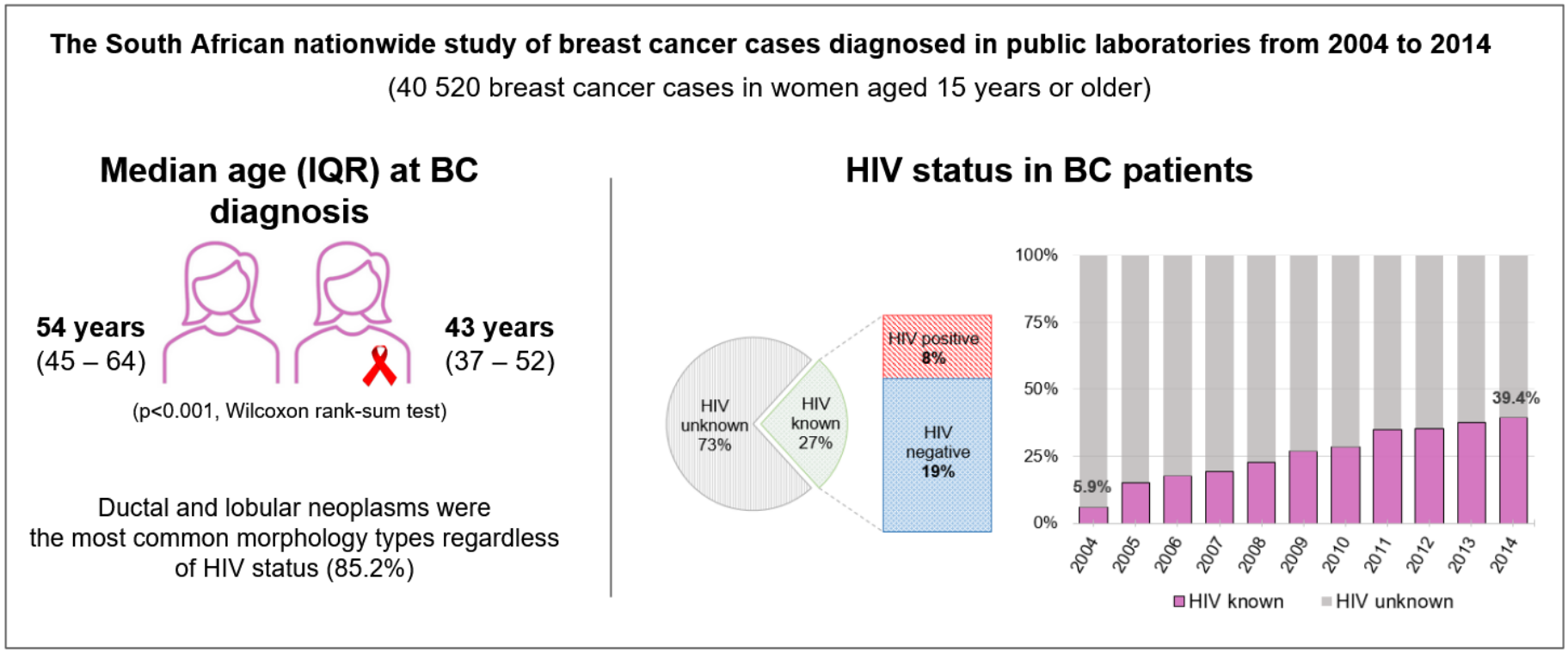


Figure 12. *The summary of the key findings from the South African nationwide study on breast cancer cases from 2004-2014*

5.3. Strengths and limitations

In this chapter, I discuss strengths and limitations of not only the individual publications presented in this thesis but also the overall strengths and limitations of my thesis.

Strengths

In my thesis, I presented four publications, each using a different study design and research method. I worked with both qualitative and quantitative data, collaborated with international agencies, and engaged with health professionals and stakeholders from sub-Saharan Africa. The overall strength of my thesis, and particularly **Section I,** is the use of a comprehensive three-step approach to evaluate the cervical cancer prevention and care continuum for women living with HIV in sub-Saharan Africa. This comprehensive work was supported by collaboration with more than 70 stakeholders from 15 countries for sub-Saharan Africa and partners from several international organizations, including the IARC and the National Cancer Institute (NCI). We developed and agreed upon a set of facility-based indicators and variables needed to inform these indicators, aiming to improve data collection on cervical cancer prevention and care services offered at HIV clinics across sub-Saharan Africa (**Publication 1**). This research was informed by results from **Publication 2** which evaluated and summarized current practices and recommendations through the review of national cancer policies. Findings from this review also informed the development of the facility-based survey to further assess program practices and the availability and utilization of services (**Publication 3**). In designing the survey, we adhered to guidelines and recommendations from the most comprehensive toolkit for cervical cancer prevention and control programs developed by WHO [72]. To date, this toolkit represents the largest and most comprehensive global effort in improving and accelerating the high-quality data availability for the planning, implementation, and improvement of global cervical cancer programs.

An additional strength of my thesis, particularly **Section II**, is the results from one of the most comprehensive study in South Africa that evaluated breast cancer cases reported to the National Cancer Registry over an eleven-year period, taking into account HIV status based on laboratory data from the NHLS. Furthermore, the inclusion of socio-economic data, based on the ward level SAIMD, facilitated by our collaboration with the University of Oxford, significantly enriched this study. This

collaboration enabled us to analyze socio-economic factors at the municipal level, providing a better understanding of breast cancer cases in women living with HIV.

Individual strengths of each publication are presented in their respective chapters within this thesis (please see Chapter 4: RESULTS AND ORIGINAL PUBLICATIONS). In brief, **Publication 1** utilized a comprehensive methodological approach that included a rigorous multidisciplinary expert panel selection process and iterative three-round Delphi process. This was supplemented with an extensive literature review of monitoring indicators, collaboration with international experts, and several online discussions, including a Virtual Stakeholder Meeting attended by 72 participants from 15 countries. These events were facilitated by professional moderators and supported by simultaneous translators to ensure that all voices were heard. Both quantitative and qualitative data were collected and analyzed. All these efforts enhanced the potential for applicability and generalizability across different contexts in sub-Saharan Africa. **Publication 2** employed an exhaustive approach to reviewing cervical cancer prevention policies in sub-Saharan Africa's countries with high HIV prevalence. Through a thorough search and data collection process, including both published and unpublished documents, as well as direct consultations with country experts, the study provides a comprehensive overview of the policy landscape. **Publication 3** utilized a survey developed based on the WHO standardized tool [72] and IARC CanScren5 [108] recommendations to gather and evaluate accurate, up-to-date information on the availability and delivery of cervical cancer control services, health information systems and program monitoring. The survey development engaged IeDEA principal investigators, data managers, nurses, and members of the CanScreen5 and WHO development teams. Additionally, during the field visits to six of the 30 sites included, situated in two of the four IeDEA African regions, the lead author collected inputs on the survey from local cervical cancer control program experts. The multidisciplinary collaborative efforts with representatives from each participating country enhanced the local relevance and validity of findings across various contexts. The survey was offered in two languages, distrusted both electronically and in paper form, and collected program data at the site level and routinely collected data at the patient level, thereby offering a comprehensive view of the actual situation in these settings. **Publication 4** was a nationwide study in South Africa that compared breast cancer cases in women living without and with HIV in the ART era. The study utilized

laboratory confirmation of both breast cancer and HIV, allowing for high specificity of these diagnoses. The NCR used probabilistic record linkage methods and text search to ensure that most of the available HIV records are extracted and matched. These methods allowed to identify records belonging to the same individual even in the absence of a unique identifier. There was a sufficient number of breast cancer cases in female population aged 15 years or older to ensure a comprehensive analysis.

Limitations

Through the journey of my PhD, I encountered several challenges that led to practical limitations of my doctoral research, mostly due to time constraints and feasibility of planned research activities. Additionally, the unexpected onset of the COVID-19 pandemic introduced unforeseen disruptions, further complicating and delaying some of the planned research activities. This included extending the IeDEA DES and testing both the core and optional indicators to measure the performance of cervical cancer prevention and care programs at the facility level in real-life settings. Despite my best efforts and collaboration with the IeDEA DES team to incorporate the necessary variables for the selected indicators, we were not able to complete this task by the end of my PhD. Moreover, my initial plan to develop a technical guide for implementing these indicators into the routine data collection practices at the facility level was postponed due to these time constraints. Nonetheless, my team and I will continue collaborating with the IeDEA DES team. We plan to test indicators on a synthetic dataset and conduct pilot studies for data collection and analysis in selected IeDEA sites. The ultimate goal is to publish a technical guide for the implementation of these indicators into facility-based monitoring practices at the IeDEA HIV clinical sites.

Here, I briefly outline some of the individual limitations of the publications that are further detailed in their respective chapters (please see Chapter 4: RESULTS AND ORIGINAL PUBLICATIONS). **Publication 1** faced some limitations, such as low response rates (34%-45%) across all Delphi rounds, which could affect the generalizability of our findings. The complexity and length of the initial questionnaire, along with the transition to online discussions due to the COVID-19 pandemic, might have reduced participants' motivation to engage. These factors highlight the challenges of involving a wider array of stakeholders and emphasize the need to minimize participant burden and carefully consider the format of their engagement in

future consensus-building efforts. The limitations of the method used in **Publication 2** are mainly related to the available policy documents, which may not fully capture current practices or the most recent policy changes, especially these that happened after April 2022, when the search was last updated. Focusing on global and national indicators for monitoring cervical cancer prevention and care services may overlook the nuances of regional or local monitoring, potentially limiting the understanding of community-specific implementation challenges and successes. Additionally, differences in expert responses might not fully reflect national policies, suggesting a gap between policy and actual practice in the surveyed countries. **Publication 3** included only girls and women living with HIV who are in care and receiving ART at the included sites. This is not necessarily representative of the broader HIV population in the respective countries, as some women may not be aware of their HIV status or may not be receiving appropriate care. Additionally, the surveyed facilities are part of the IeDEA consortium, which receives research funding, potentially affecting the representativeness of our findings in the wider context of cervical cancer prevention and care in these countries. Our study was limited to an intentional subset of sites known for their advanced cervical cancer prevention and care programs, further narrowing the applicability of our findings. Furthermore, changes in service delivery and monitoring efforts since our data collection may impact the current relevance of our findings at some of the sites we studied. **Publication 4** encountered several methodological limitations, particularly the potential underreporting of breast cancer cases, as the South African National Cancer Registry is pathology-based. That means that diagnoses made radiologically or clinically only are not reported to the National Cancer Registry. The analysis included breast cancer cases reported from up to 2014, which may not accurately reflect current trends and advancements in breast cancer control in South Africa. Also, the data lacked clinical and patient information relevant to breast cancer risk factors, and the HIV status for many patients was unknown, introducing possible selection bias and limiting generalizability of our findings. Additionally, the method used to describe socioeconomic parameters was based on the laboratory location where the breast cancer was diagnosed and the corresponding municipality, which may not accurately represent the individual socioeconomic circumstances of the patients.

5.4. Implications for policy and directions for future research

Implications and interpretation of findings

The ACCHIVe project, along with **Publications 1, 2, and 3** that resulted from it, has contributed to the understanding of cervical cancer prevention and care, particularly highlighting the efforts and gaps for women living with HIV in sub-Saharan Africa.

In **Publication 1**, I introduced the 17 internationally agreed-upon indicators specifically designed for HIV clinics that provide cervical cancer prevention and care services to women living with HIV. These indicators aim to improve the collection of high quality, standardized data for decision-making processes and future policy development. By using a standardized set of indicators and variables to measure program performance, we can uncover inequities and disparities in cervical cancer prevention and care among women living with HIV, and identify service gaps within countries and regions. This information may guide future efforts and investments at both the local and national level to further enhance prevention and care programs. These indicators are a valuable addition to the current global WHO efforts to monitor and evaluate the progress towards cervical cancer elimination. Although these indicators are specifically designed for cervical cancer prevention and care programs offered to women living with HIV, the knowledge gained from this research can also enrich and inspire monitoring efforts for breast and other cancer prevention and care services in sub-Saharan Africa. **Publication 2** revealed a lack of uniform recommendations for cervical cancer prevention and care for girls and women living with HIV across sub-Saharan African countries with high HIV burden. Specifically, it found variations in the recommended age for screening imitation and the rescreening intervals for women living with HIV. Additionally, despite WHO recommendations for HPV DNA testing, policies more frequently reported other screening methods. Recommendations for treating invasive cancer in women living with HIV, monitoring indicators disaggregated by HIV status, and the costs of services for clients were rarely reported. To address these gaps, enhanced monitoring of cervical cancer prevention and care programs and increased advocacy are essential. Such efforts can build the evidence needed to urge governments to develop, fund, and implement comprehensive cancer control plans. Future cancer control policies should include recommendations for high risk populations, including girls and women living with HIV. This is especially important

given the increased risk of cervical cancer in women living with HIV compared to the general population, along with their increased susceptibility to recurrent cervical lesions and cervical cancer. Significant advancements have been made since the global strategy to eliminate cervical cancer was adopted three years ago, yet critical action is still needed to reach global targets. Since then, the number of countries that have implemented HPV vaccination program has been increased to total 140 countries – of which 27 are in Africa. Worldwide, the percentage of 15 years old girls received the recommended doses of HPV vaccine has improved by 10% – from 2% in 2010 to 12% in 2021 [113]. At the time of our study presented in **Publication 3**, only a third of the investigated sites were offering HPV vaccination, and data to estimate the HPV vaccination rates in girls living with HIV were scare. The latest evidence suggests that single-dose bivalent and nonavalent HPV vaccines are highly effective, similar to multidose regimes, in preventing persistent oncogenic HPV infections in young African women [114]. This not only promises to improve coverage rates among young women but also allows for easier integration into existing health service delivery models. Furthermore, one-dose approach could lead to substantial cost savings, making the HPV vaccines more affordable and potentially increasing their availability to a wider population. **Publication 3** has also demonstrated a wide gap between WHO's cervical screening and treatment targets (70% screening and 90% treatment of screen-positive women) and the actual rates observed in several HIV clinics, both with on-site and off-site cervical cancer control services. Particularly in sub-Saharan Africa, screening rates are alarmingly low, with only 15%of women aged 30-49 years reporting having been screened for cervical cancer [115] in 2019, and 16.9% (country-level median) in 2020 [116]. Recent systematic review estimated that 30% of women living with HIV aged 25 to 49 years had ever been screened for cervical cancer in 2020, compared to 11% of women without HIV [117]. Overall, the screening rates for cervical cancer in sub-Saharan Africa remain far below optimal levels, affecting both the general population and women living with HIV. **Publication 3** reported that VIA is the preferred screening method in many facilities, chosen for its low resource requirements and the ability to provide immediate treatment, thus keeping women engaged in care. Shifting to more advanced HPV/DNA testing, as recommended by WHO, despite its advantages, demands significant improvements in laboratory infrastructure, quality assurance, and funding, especially within the context of sub-Saharan Africa's fragile healthcare systems [118]. **Publication 3** also highlighted critical infrastructure and

financial challenges hindering cervical cancer prevention and care for women living with HIV across sub-Saharan Africa. The adoption of WHO's recommended screen-triage-treat strategies for women living with HIV is challenging due to local infrastructure deficits and financial limitations. To overcome these obstacles and increase the HPV vaccination and cervical screening uptake, strong political will and commitment is needed. Partnerships aiming to improve national strategies, increase budgets for cervical cancer prevention, and enhance advocacy and civil society involvement, are the key to achieving the WHO targets.

Publication 4 provided important evidence on the characteristics of breast cancer in South African women, living with or without HIV, diagnosed from 2004 to 2014. The study found that the median age at breast cancer diagnosis was 10 years lower in patients living with HIV compared to those without HIV, which can be explained by the generally younger age distribution within the population living with HIV. It also found that black breast cancer patients were disproportionately affected by HIV compared to patients of other ethnicities, mirroring the broader HIV epidemic in South Africa. Throughout the study period, there was a substantial improvement in the recording of HIV status, with known statuses rising from 5.9% in 2004 to 39.4% in 2014. However, the HIV status remained unknown for 73.4% of breast cancer patients. As the population living with HIV ages, we can expect a growing burden of breast cancer in this population, potentially impacting not only the health and quality of life of women with HIV but also straining the healthcare system and its professionals. In South Africa and other high-HIV-burden countries, breast cancer patients newly diagnosed and unaware of their HIV status should be offered HIV testing to ensure comprehensive management. Moreover, a deeper understanding of patient-, cancer-, and municipality-related characteristics could uncover disparities and gaps in breast cancer prevention and care, particularly for women living with HIV. A potential first step in mitigating these disparities is rising awareness about breast cancer and integrating breast cancer prevention and diagnostic services within established HIV clinics.

Future perspectives

In order to extend our impact of the findings presented in **Publication 1** beyond scientific meetings and journals, my team is supporting the IeDEA DES working group members to incorporate the minimum dataset of variables needed to collected and reported into IeDEA DES to inform core indicators. Integrating these indicators into IeDEA DES will facilitate the standardized data collection and reporting within IeDEA Consortium and four African regions. Additionally, there are ongoing efforts to test variables and indicators using simulated datasets. This dataset will present real-life scenarios within the cervical cancer care continuum and train relevant stakeholders in collecting and analyzing specific data. Future efforts should focus on implementing these variables and indicators into routine data collection practices at HIV clinics that are part of the IeDEA network, as well as identifying factors that affect the implementation and feasibility to collect specific data. We encourage other researchers and data managers to implement these variables and indicators at facility level to better understand the gaps and bottlenecks within their cervical cancer prevention and care continuum. Leveraging implementation science theories, strategies and frameworks can significantly support monitoring efforts, potentially yielding additional evidence that contributes to the success of future cancer screening programs in sub-Saharan Africa. **Publication 2** found that although all selected countries had cancer control policies covering aspects of cervical cancer prevention and care, there was considerable variation in the recommendations and practices, particularly for women living with HIV. Policymakers should consider updating current cancer control policies to include evidence-based recommendations specifically tailored for girls and women living with HIV. Future research should explore strategies to overcome financial and infrastructure barriers in cervical cancer prevention and care for women living with HIV, as highlighted in **Publication 3**. It is crucial for cervical cancer prevention and care programs to be adequately funded and for screening and treatment services to be offered free to patients to ensure high participation rates. Countries need to invest in collecting population-level data to estimate cervical cancer screening coverage and evaluate other performance indicators. The future of cervical cancer prevention lies in HPV/DNA testing and HPV vaccination. Exploring how HPV DNA testing and triage can be incorporated into existing screening programs and assessing the impact on screening rates are vital steps. De-implementation studies

aimed at discontinuing ineffective interventions, such as VIA screening, could facilitate a smoother transition towards HPV DNA testing. Additionally, cost-effectiveness analyses of the recommended prevention and care strategies are needed, along with clinical trials to investigate the comparative effectiveness and feasibility of HPV DNA testing versus other, more commonly used, screening methods. Research into factors influencing HPV vaccine uptake is also important, including understanding vaccination hesitancy from social, cultural, religious, and personal perspectives. Manufacturing HPV vaccines in LMICs, potentially leveraging vaccine production capabilities developed during the COVID-19 pandemic, could ensure more equitable access to these vaccines [119].

As an overarching activity of the ACCHIVe Project, I aimed to translate our scientific knowledge into practical formats that are applicable and accessible to stakeholders and policymakers in sub-Saharan Africa. The strategy led to the publication of a policy brief (please see Supplementary Chapter 10.2, available at https://k4d.ch/facility-based-indicators-to-monitor-cervical-cancer-control-services-for-women-living-with-hiv/) and the Swiss TPH project brochure (available at https://issuu.com/communications.swisstph/docs/cervical_cancer_brochure_final). In the policy brief, I provided more information on the Cervical Cancer Prevention and Care Cascade and explained the aims and implications of this framework. I also outlined the five core and 12 optional indicators and the minimum set of data elements required to inform these indicators. We promoted the policy brief through various channels to reach a wider audience and shared it within the IeDEA consortium. Furthermore, to facilitate knowledge sharing, we made all (nine) presentations from the Virtual Stakeholders Meeting publicly available at a community-led digital archive, AfricArxiv (available at: https://africarxiv.figshare.com/search?itemTypes=2). These videos have been watched 1 017 times and downloaded 160 times since they were posted (data as of April 2024). These activities taught me about the importance of communication and dissemination strategies, including the use of various tools like social media, to facilitate open access and knowledge sharing. By making scientific evidence more accessible and engaging through platforms commonly used by the public and local communities, researchers can significantly broaden the reach and applicability of their findings. This strategic approach not only enhances the visibility of research outcomes but also serves as a critical bridge, translating complex scientific

insights into actionable knowledge for diverse audiences. Therefore, I strongly encourage the scientific community to consider these communication and dissemination methods as standard practices in research and knowledge sharing.

Our collaboration with the research team at the South African National Cancer Registry, which formed the basis of **Publication 4**, is still ongoing, with several promising projects in progress. Currently, the team is linking cancer data with NHLS data for the period after 2014 to further explore cancer patterns and trends in individuals living with HIV in South Africa. Future research should more thoroughly investigate breast cancer survival and mortality among women living with HIV, by utilizing linkage methods and integrating various data sources. This is of particular importance, given that breast cancer survival rates in sub-Saharan Africa are among the lowest globally [30, 61]. Moreover, future efforts should focus on identifying innovative interventions for the prevention and early detection of breast cancer, aiming to address disparities, particularly among women living with HIV. The GBCI offers evidence-based guidelines for the staged implementation of such interventions, alongside with recommendations how to strength health systems, evaluate and enhance early detection and management for breast cancer.

6. CONCLUSION

This thesis contributed towards filling the knowledge gaps in the field of cervical and breast cancer prevention and care for women living with HIV in sub-Saharan Africa. It offers insights and inspiration for further studying evidence-based interventions to implement and scale up cervical and breast cancer prevention and care programs for women living with HIV in sub-Saharan Africa.

It presented four publications I authored and co-authored, and reflected my research effort in the last few years. I led the development of 17 indicators and its minimum data set to monitor the performance cervical cancer prevention and care services offered to women living with HIV in sub-Saharan Africa. I participated in the review of cancer control policies that has shown the progress in cervical cancer control policy development in sub-Saharan Africa. However, it discovered that specifications for girls and women living with HIV were lacking or varied within the countries with the highest burden of HIV in this region. I participated in the facility-based survey that provided the knowledge and identified the gaps in cervical cancer prevention and care provision

and its outcomes at HIV clinics in sub-Saharan Africa. The findings revealed that persistent infrastructural and financial challenges were the major barriers to access and utilization of the cervical cancer prevention and care services. The survey also assessed the monitoring efforts and found that data to monitor global cervical cancer elimination targets were uncommon across clinics despite the wide availability of electronic systems. Even when data was available, most sites reported progress below the defined WHO targets. And last, I provided insights on patient-, cancer-, and municipality-related characteristics from the nation-wide study of breast cancer in women living with and without HIV diagnosed in public health sector in South Africa from 2004 to 2014. With these findings, I contributed knowledge to better understand the double burden of HIV and breast cancer in South African women.

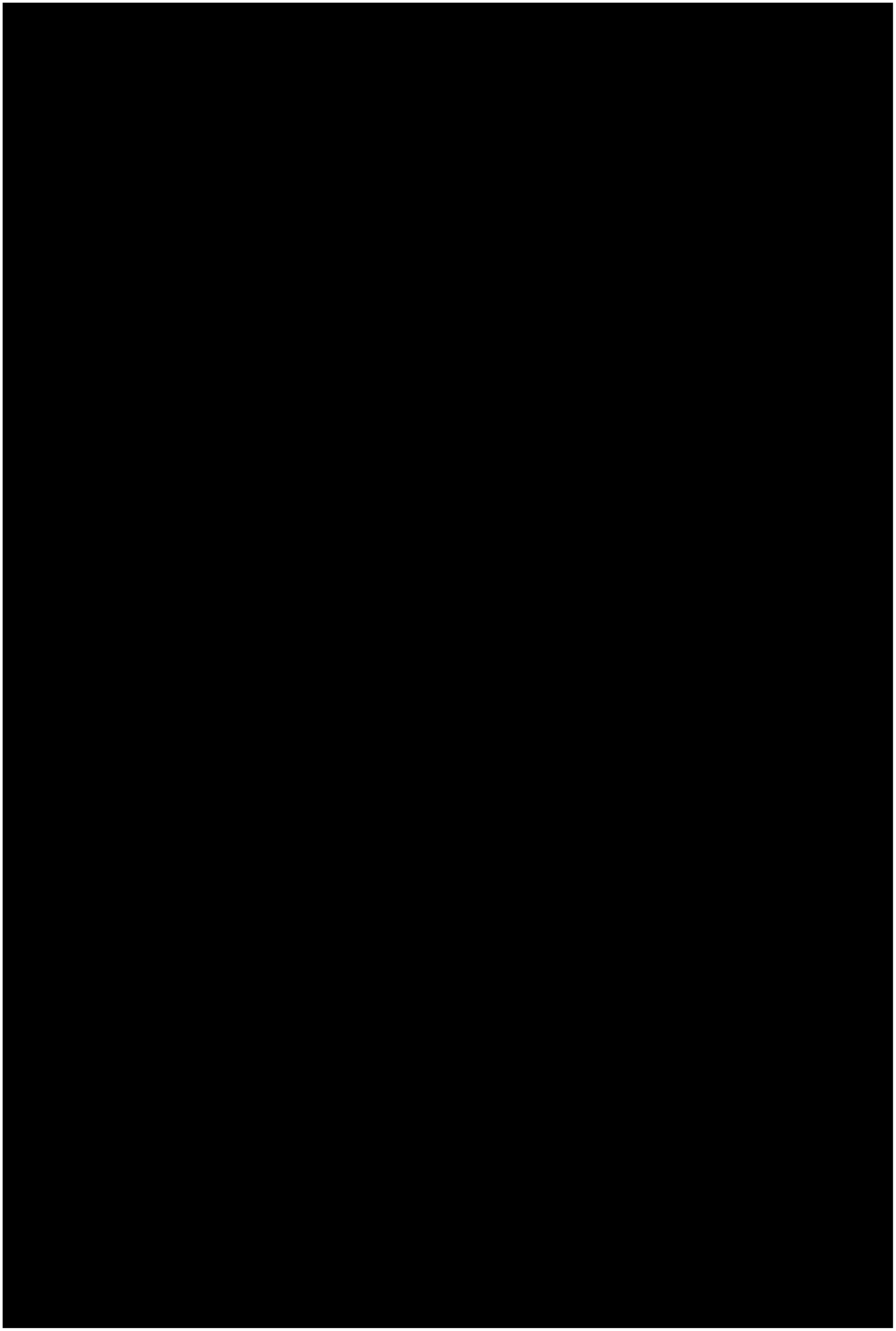
The main focus of my thesis were women living with HIV in sub-Saharan Africa. Unfortunately, this region faces the highest HIV prevalence and incidence in the world. There is still a lot to be done, but the path to ending AIDS is well known and includes strong national leadership and political commitment, investment in evidence-based HIV prevention, testing, and treatment programs, and multidisciplinary and multinational collaboration. The cancer burden in sub-Saharan Africa is high, and with the expected aging of women living with HIV, breast and cervical cancer burden is growing. The WHO launched two global initiatives, **Cervical Cancer Elimination Initiative** and **Global Breast Cancer Initiative**, which provide recommendations for a comprehensive approach to addressing and treating these health challenges. Accelerating the implementation of these initiatives and investing wisely in interventions that are affordable and effective has the potential to prevent many deaths. Ministries have to set country-specific priorities that are feasible, evidence-based and can be financed and have national cancer plans in place. Countries should focus on feasible strategies, such as cervical screening, HPV vaccination, or strategies to promote early diagnosis and treatment for curable cancers. All these efforts should be accompanied by robust information systems and monitoring that are needed to inform decision-making. Communities and civil societies can provide great support in increasing the implementation of cancer prevention and care services.

Cervical cancer elimination and breast cancer control can only be achieved through a multi-sectoral and integrated approach across the cancer prevention and care continuum. In sub-Saharan Africa, cervical cancer can be eliminated (fewer than four

women per 100,000 women-years) with a high coverage of HPV vaccination and cervical screening. It is essential that HPV vaccination is incorporated into all national immunization programs, and enhancing access and availability of HPV vaccination for all girls is imperative. To address the significant disparities in cervical screening coverage in this region, evidence-based interventions such as the expansion of screening through self-sampling methods, together with community engagement and educational campaigns, are crucial to ensure access for all women, regardless of their HIV status. For breast cancer control, prioritizing the implementation and expansion of early detection programs and the downstaging of breast cancer diagnoses is vital. Strategies for early detection programs should be tailored to the health system's readiness at national and/or subnational levels. Successful implementation of these programs requires the capacity not only to diagnose patients with symptomatic breast findings or other clinically detectable abnormalities but also to provide comprehensive treatment.

Addressing cervical and breast cancer in women living with HIV in sub-Saharan Africa requires a comprehensive approach that navigates the unique challenges arising from the intersection of these chronic conditions. This involves not only advancing our understanding and using tailored interventions for the prevention, diagnosis, and timely treatment of co-morbidities but also enhancing healthcare infrastructure, increasing awareness, mitigating stigma, and integrating cancer prevention and care services within ART programs to improve access and outcomes. Moreover, these initiatives must be complemented by efforts to enhance data collection and monitoring of cancer prevention and care programs. Such efforts are crucial for gaining insights into the specific needs of this population, evaluating the efficacy of interventions, and identifying any potential disparities in service provision.

Cervical cancer elimination and breast cancer control is a gender-equity and human rights imperative. Women have a central roles in our societies, and protecting women from cancer also protects their families, communities, and the economy as a whole. A context-specific approach to primary, secondary, and territory prevention of cervical and breast cancer is essential for reducing the burden of these diseases in sub-Saharan Africa. This involves implementing sustainable, cost-effective, and equitable strategies at the individual, community, health system, and population level within all steps of the cancer prevention and care continuum.



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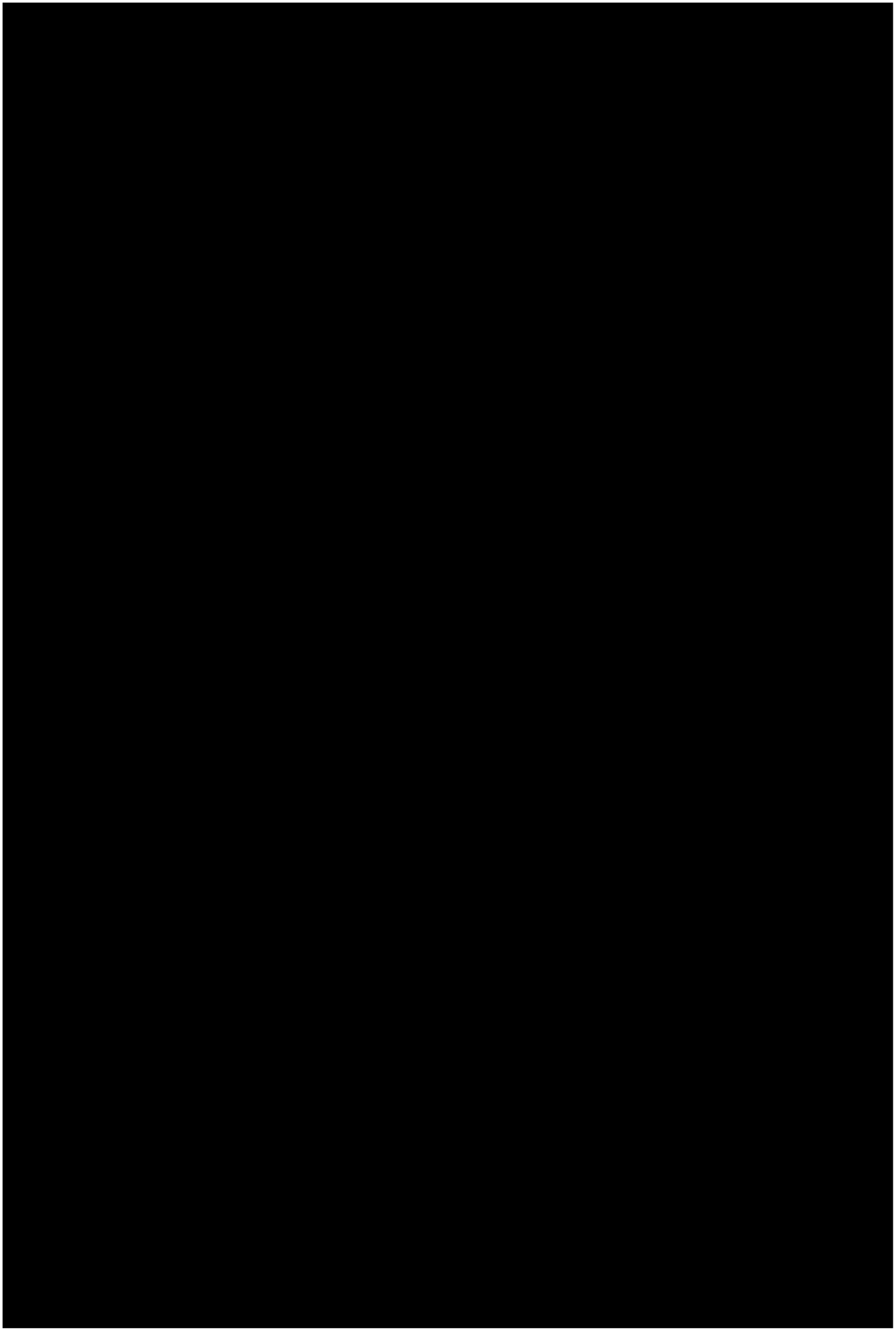

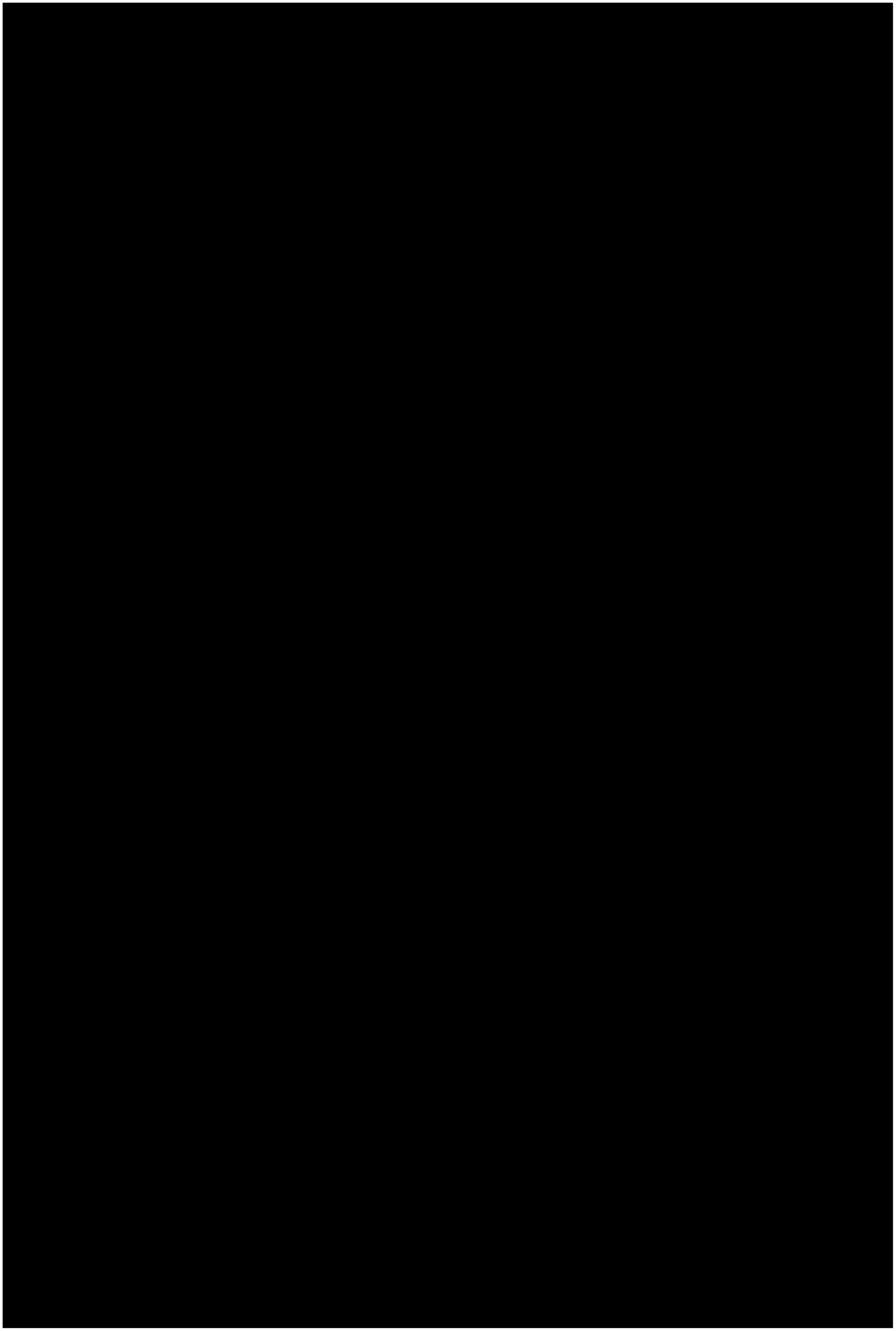

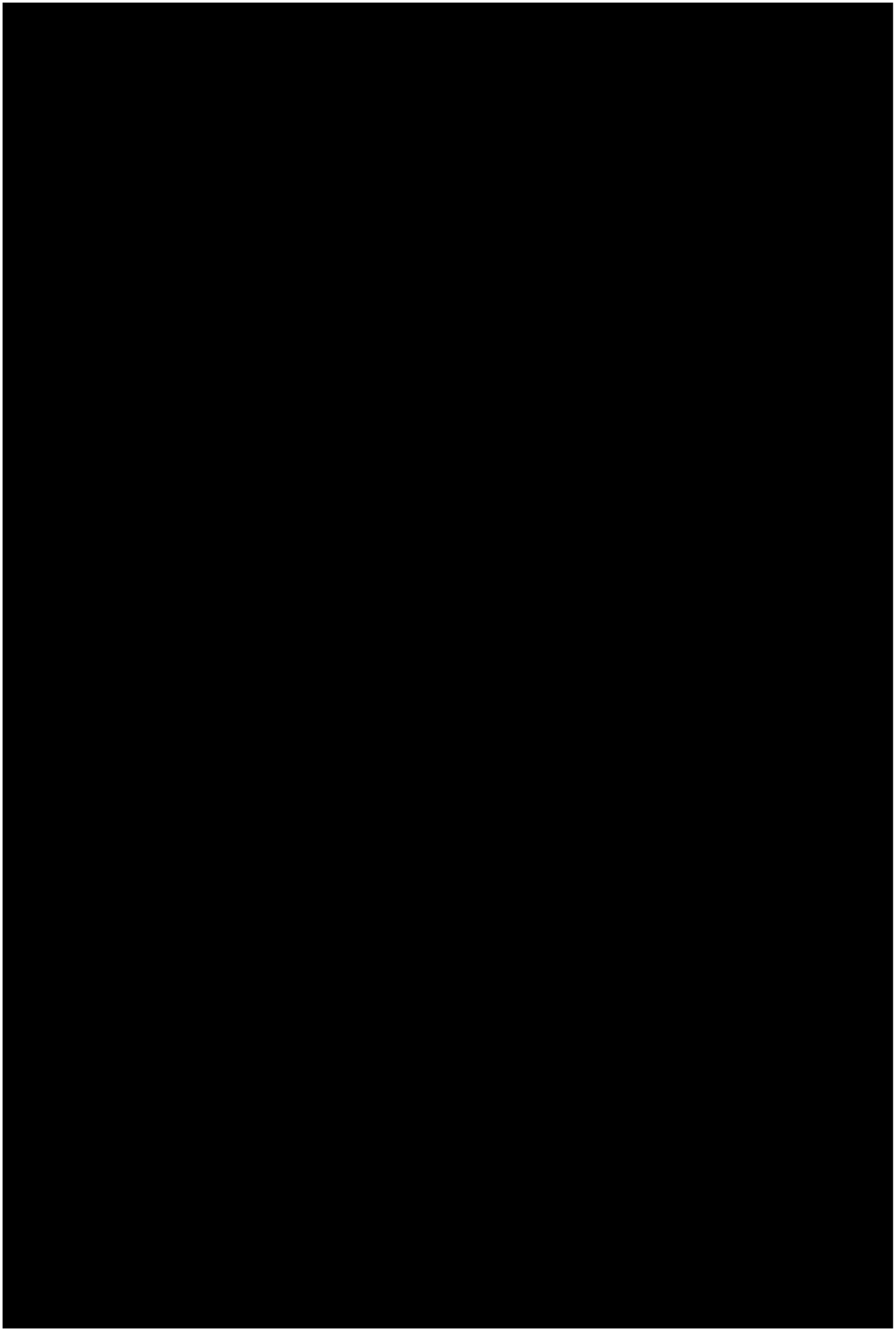

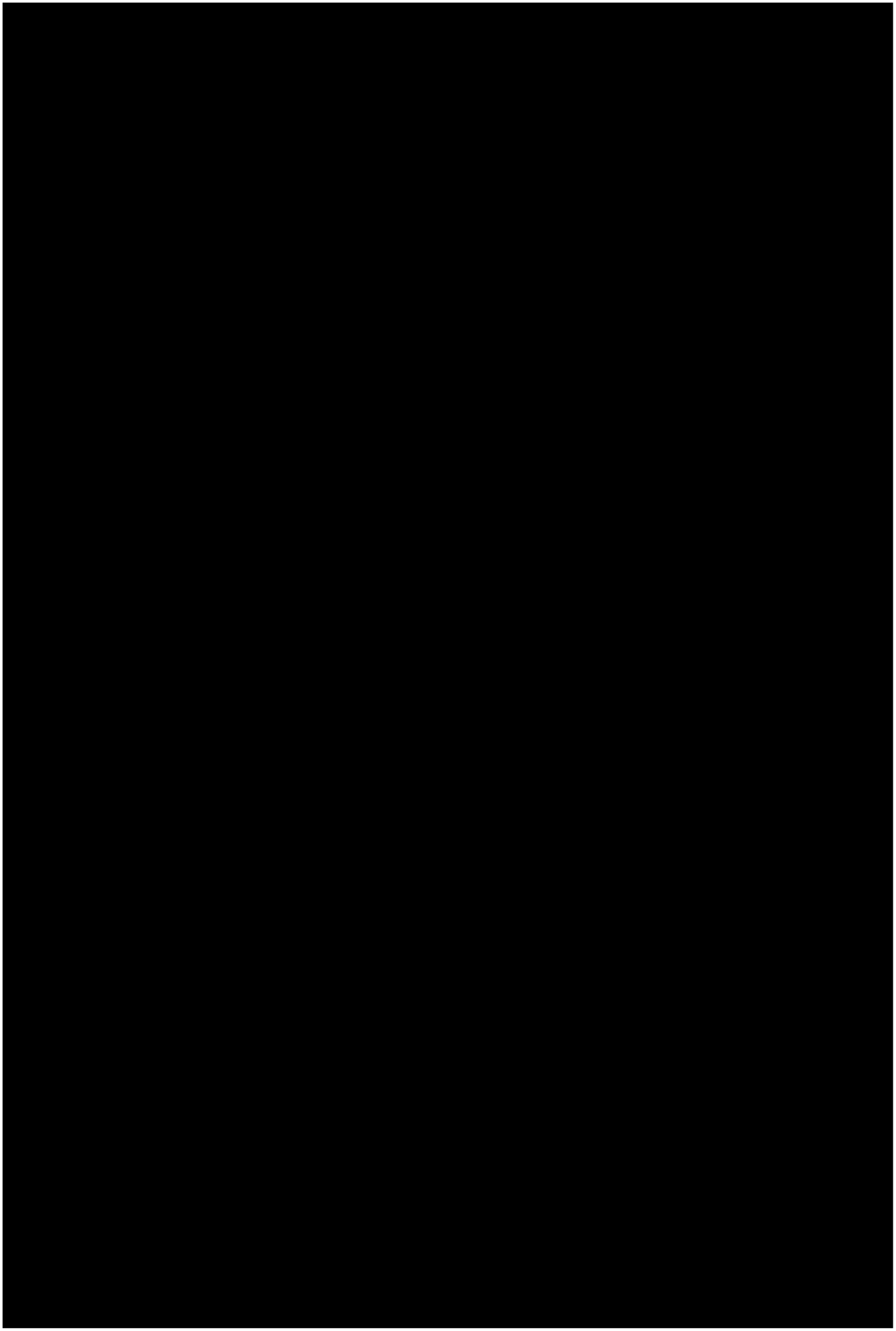

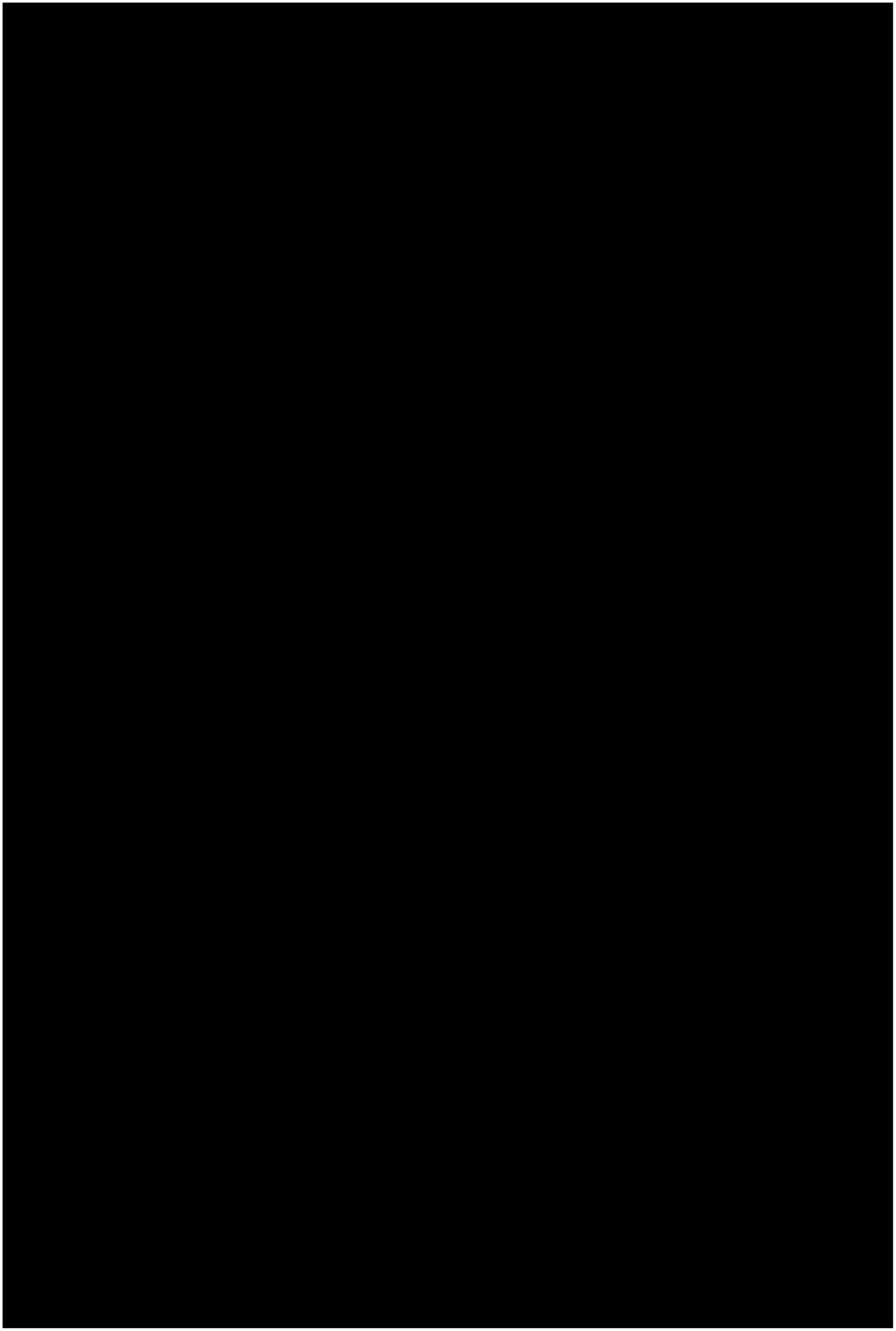

8. COMPLETE LIST OF PUBLICATIONS

Published articles

1. Asangbeh-Kerman SL, **Davidović M**, Taghavi K, Dhokotera T, Manasyan A, Sharma A, Jaquet A, Musick B, Twizere C, Chimbetete C, Murenzi G, Tweya H, Muhairwe J, Wools-Kaloustian K, Technau KG, Anastos K, Yotebieng M, Jousse M, Ezechi O, Orang'o O, Bosomprah S, Boni SP, Partha B, Bohlius J; International Epidemiology Databases to Evaluate AIDS. Cervical cancer prevention and care in HIV clinics across Sub-Saharan Africa: results from a facility-based survey. J Int AIDS Soc. 2024 Jul;27(7):e26303. https://doi.org/10.1002/jia2.26303
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1. **Davidović M**, Asangbeh SL, Taghavi K, Dhokotera T, Jaquet A, Musick B, Van Schalkwyk C, Schwappach D, Rohner E, Murenzi G, Wools-Kaloustian K, Anastos K, Omenge OE, Boni SP, Duda SN, von Groote P, Bohlius J; International Epidemiology Databases to Evaluate AIDS. Facility-Based Indicators to Manage and Scale Up Cervical Cancer Prevention and Care Services for Women Living With HIV insSub-Saharan Africa: a Three-Round Online Delphi Consensus Method. Poster session presented at: 14th Symposium Graduate School for Health Sciences 2022; Nov 28 – 30, 2022; Gerzensee, Switzerland
2. **Davidović M**, Asangbeh SL, Taghavi K, Dhokotera T, Jaquet A, Musick B, Van Schalkwyk C, Schwappach D, Rohner E, Murenzi G, Wools-Kaloustian K, Anastos K, Omenge OE, Boni SP, Duda SN, von Groote P, Bohlius J; International Epidemiology Databases to Evaluate AIDS. Cervical Cancer Prevention and Care Indicators for Women Living with HIV in Africa. Poster session presented at: The Swiss Public Health Conference 2023; Sept 12 – 13; Lausanne, Switzerland.
3. **Davidović M**, Asangbeh SL, Taghavi K, Dhokotera T, Jaquet A, Musick B, Van Schalkwyk C, Schwappach D, Rohner E, Murenzi G, Wools-Kaloustian K, Anastos K, Omenge OE, Boni SP, Duda SN, von Groote P, Bohlius J; International Epidemiology Databases to Evaluate AIDS. Cervical Cancer Prevention and Care Indicators for Women Living with HIV in sub-Saharan Africa: Delphi Method. Poster session presented at: World Cancer Congress; Oct 18 – 20, 2022; Geneva,

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10. SUPPLEMENTARY CHAPTERS

In the following chapters, I introduce two peer-reviewed published publications and two non-peer reviewed publications that provide additional insight in my PhD topic and contribute further understanding to my research efforts. Dhokotera TG et al. explored the incidence of and risk factors for developing breast and gynecologic cancers amongst women living with HIV in South Africa. This study provided a foundation evidence for further exploration of breast cancer cases and patient-, cancer-, and municipality-related characteristics in South African women living with and without HIV, presented in Chapter 0. Reffieux Y et al. analyzed the associations between immunodeficiency and cancer incidence, including cervical and breast cancers in a nationwide cohort of people living with HIV in South Africa. This study provided a better understanding of the impact of immunodeficiency on the risk of cervical and breast cancer.

1. Dhokotera TG, Muchengeti M, **Davidović M**, Rohner E, Olago V, Egger M, Bohlius J. Gynaecologic and breast cancers in women living with HIV in South Africa: A record linkage study. Int J Cancer. 2024 Jan 15;154(2):284-296. https://doi.org/10.1002/ijc.34712
2. Ruffieux Y, Muchengeti M, Egger M, Efthimiou O, Bartels L, Olago V, **Davidović M**, Dhokotera T, Bohlius J, Singh E, Rohner E. Immunodeficiency and Cancer in 3.5 Million People Living With Human Immunodeficiency Virus (HIV): The South African HIV Cancer Match Study. Clin Infect Dis. 2021 Aug 2;73(3):e735-e744. https://doi.org/10.1093/cid/ciab087

I also present two non-peer review publications, of which one is a **policy brief** that has been a result of my additional role in the last few months of PhD trajectory, when I was responsible to develop communication and dissemination strategy required by our funders (r4d, SNSF) for the ACCHIVe project. The policy brief presents the overview of indicators and the minimum data set needed to inform these indicators that resulted from the Delphi consensus process presented in Chapter 4.1. The second publication I co-authored is a **scoping review protocol** that has been published at Africa AfricArXiv and provides relevant information and additional context to the work presented in Chapter 4.2.

1. **Davidović M** and Bohlius J, on behalf of the IeDEA. Facility-based indicators to monitor cervical cancer control services for women living with HIV. R4d Policy Brief 2023, No. 1, December 2023. Available from: https://k4d.ch/facility-based-indicators-to-monitor-cervical-cancer-control-services-for-women-living-with-hiv/
2. Asangbeh SL, Taghavi K, **Davidović M**, Bohlius J. Indicators and targets for cervical cancer prevention in countries with the highest HIV burden: A scoping review protocol. AfricArXiv [Internet]. 2022 Apr 14; Available from: https://africarxiv.pubpub.org/pub/argxh98c

10.1. Other Relevant Peer-Reviewed Publications

Gynaecologic and breast cancers in women living with HIV in South Africa: A record linkage study

Published as:

Dhokotera TG, Muchengeti M, **Davidović M**, Rohner E, Olago V, Egger M, Bohlius J. Gynaecologic and breast cancers in women living with HIV in South Africa: A record linkage study. International Journal of Cancer. 2024 Jan 15;154(2):284-96. https://doi.org/10.1002/ijc.34712

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I contributed towards the study design and data interpretation. I provided comments on the first and subsequent drafts of the manuscripts.

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RESEARCH ARTICLE

Cancer Epidemiology

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Gynaecologic and breast cancers in women living with HIV in South Africa: A record linkage study

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Abstract

Breast and gynaecologic cancers account for approximately half of all cancers diagnosed amongst women in South Africa, many of whom also live with HIV. We aimed to determine the incidence of and risk factors for developing breast and gynaecologic cancers in women living with HIV (WLHIV) in South Africa. This is a longitudinal analysis of the South African HIV Cancer Match study including women aged ≥15 years with two or more HIV-related laboratory tests. We used Cox proportional hazard models to determine the association of Human Papilloma Virus (HPV)-related and hormone-related gynaecologic cancer with patient- and municipal-level characteristics. From 3 447 908 women and 10.5 million years of follow-up, we identified 11 384 incident and 7612 prevalent gynaecologic and breast cancers. The overall crude incidence rate was 108/1 00 000 person-years (pyears) (95% confidence interval [CI]: 106-110), with the highest incidence observed for cervical cancer (70/1 00 000 pyears; 95% CI: 68.5-71.7). Low CD4 cell counts and high HIV RNA viral loads increased the risk of cervical and other HPV-related cancers. Age was associated with both HPV-related and hormone-related cancers. Women accessing health facilities in high socioeconomic position (SEP) municipalities were more likely

Abbreviations: ART, antiretroviral treatment; HPV, human papilloma virus; ICD-O-3, international classification of diseases for oncology version 3; NADC, non-AIDS defining cancer; NCR, National Cancer Registry; NHLS, National Health Laboratory Service; SAM, South African HIV cancer match study; SEP, socioeconomic position; WLHIV, women living with HIV.

to be diagnosed with HPV-related cancers and breast cancer than women accessing care in low SEP municipalities. It is important to improve the immunologic status of WLHIV as part of cancer prevention strategies in WLHIV. Cancer prevention and early detection programmes should be tailored to the needs of women ageing with HIV. In addition, SEP disparities in cancer diagnostic services have to be addressed.

KEYWORDS
epidemiology, Gynaecologic cancer, HIV, HIV RNA viral load, socioeconomic position

What's new?

Women living with HIV are at increased risk of cancers associated with human papillomavirus (HPV), such as cervical cancer. Here, the authors set out to determine the incidence and risk factors for gynaecological and breast cancers amongst women in South Africa living with HIV. Women in higher socioeconomic status municipalities were more likely to be diagnosed with breast cancer or HPV-related cancers, they found. Low CD4 counts and high HIV RNA viral loads also increased the risk of developing HPV-related cancers.

1 | INTRODUCTION

Breast and gynaecologic cancers account for approximately half of all cancers diagnosed amongst women in South Africa with breast, uterine and cervical cancer a part of the top five cancers affecting women in the country.[1] Women living with HIV (WLHIV) are at an increased risk of Human papillomavirus (HPV)-related gynaecologic cancers, such as cervical, vulvar and vaginal cancers, compared to HIV-negative women.[2,3] Although the risk of breast, ovarian and uterine cancers has not been associated with HIV, research has shown that the incidence of non-AIDS defining cancers (NADCs) has increased 3fold in recent years amongst people living with HIV.[4] This has been partially attributed to improved longevity resulting from the expanded access to antiretroviral treatment (ART) leading more WLHIV to survive long enough to develop age-related NADCs.[4,5] Besides, social determinants of health play an important role in cancer epidemiology and management, especially in low- and middle-income countries, such as South Africa.[6] Women with low socioeconomic position (SEP) have been observed to have less access to cancer care and at a higher risk of cancer compared to women with high SEP.[7]

In South Africa, HIV disproportionately affects women with a high prevalence of 17% across all ages ranging from 2.6% amongst females aged 5 to 14 years peaking at 33.3% in women aged 25 to 49 years before dropping to 13.3% in women aged 50 years and older.[8] On the other hand, breast and gynaecologic cancers make up about 50% of the new cancer cases in women. Cancer of the cervix and breast are the first and second most common causes of cancer related mortality amongst women in South Africa, respectively.[9] However, there are still gaps in information especially on the prevalence, incidence as well as risk factors for breast, ovarian and uterine cancers amongst WLHIV in South Africa. With a substantial population of women now ageing with HIV, it becomes important to understand not only HIV-related cancers but also age-related cancers in WLHIV. To assess the incidence and risk factors of cancer in people living with HIV, the South African HIV Cancer Match (SAM) study was developed.[10] This is a national HIV cohort created from routinely collected HIV data and linked to the national cancer registry data. Using this HIV cohort, we aimed to determine the incidence rate of and risk factors for developing cervical cancer and other HPV-related cancers as well as breast cancer and other hormone-related cancers in WLHIV in South Africa.

2 | METHODS

2.1 | Study design and participants

This was a longitudinal analysis of a record linkage study, including WLHIV receiving HIV care in South Africa. We used data from the SAM study, a nationwide cohort of people living with HIV.[10] The study is described in detail elsewhere.[10] Briefly, the SAM cohort is built from HIV-related laboratory records from the National Health Laboratory Service (NHLS) and cancer records from the National Cancer Registry (NCR) in South Africa. The NHLS is a network of laboratories providing its services to public sector hospitals in South Africa. The NHLS serves approximately 80% of the South African population.[11] The pathology-based NCR provided data on cancer cases. From the SAM cohort, we included women aged 15 years and older with at least two HIV-related laboratory records between 2004 and 2014.[10]

2.2 | Variables and data sources

2.2.1 | Outcome

The main outcome was breast and gynaecologic cancer diagnosis in WLHIV. Cancer cases were identified through privacy preserving probabilistic record linkages with the cancer cases recoded in the NCR. The NCR was initially established in 1986 as a pathology-based

registry, meaning it collected data for all cancers diagnosed by cytology, histology, bone marrow aspirate and trephine. In 2011, a mandate was introduced requiring both private and public healthcare facilities, including laboratories, to report diagnosed cancer cases to the NCR. The date of specimen collection was considered the date of cancer diagnosis. We estimated incidence rates of the following cancers according to the International Classification of Diseases for Oncology version 3 (ICD-O-3)[12]: cancers of the cervix (C53), other HPV-related cancers: vulva (C51), vagina (C52); breast (C50) and other hormone-related cancers: uterus (C54), ovary (C56.9); as well as other gynaecological cancers, that is, placenta (C58.9).

2.2.2 | Exposure variables

All women included in the analyses were HIV-positive. In the SAM cohort, patients were considered HIV-positive if they had test done (HIV RNA viral load or CD4 cell counts) to monitor ART or if they had a positive HIV diagnostic test (ELISA, Western Blot, or Rapid test).[10] To explore risk factors for developing HPV-related or hormone-related cancers in WLHIV, we included CD4 cell counts, HIV RNA viral loads, baseline age, calendar period at patient level; and socio-economic position (SEP) and settlement type at facility level. We used the first ever CD4 cell count or HIV RNA viral load recorded for the patient defined as the date of the first ever HIV diagnostic or monitoring test. We grouped CD4 cell counts as follows: ≤200, 201 to 350, 351 to 500 and >500 cells/μl. We grouped HIV RNA viral loads into two groups: <1000 and ≥1000 copies/ml to reflect suppressed vs unsuppressed HIV RNA viral loads as defined in the South African National HIV survey.[8] Baseline age was defined as the age at first HIV-related laboratory record in our analysis and grouped into 10-year age groups apart from those 15 to 19 years and those over 60 years. Calendar period was determined from baseline and divided to reflect the changes in HIV testing and treatment policies in South Africa: 2004 to 2007 early ART period, 2008 to 2010 middle ART period and 2011 to 2014 late ART period.[13-15] Information on individual SEP or residential address was unavailable in the NHLS laboratory records. Therefore, to determine the SEP we used information on the facility of HIV test and the associated multiple deprivation rank of the municipalities hosting the respective facilities.[16] Deprivation in this context is defined as the unmet needs of people. We used the South African Index of Multiple Deprivation, a ward level weighted aggregate of four dimensions of deprivation derived from the Statistics South Africa census data.[16] These dimensions include material, employment, education and living environment deprivation. To determine the municipal level ranking, we used population weighted average of ward ranks. The most deprived municipality (low SEP) was given a rank of one whilst the highest rank was given to the least deprived areas (high SEP). We also used the municipality information to define the health facility as rural or urban settlement. Data on municipal settlement type was determined from the national data dictionary.[17]

2.3 | Statistical methods

We described the patient characteristics stratified by prevalent, incident or no cancer. We defined prevalent cancers as those occurring on or before the first HIV-related test whilst incident cancer cases were defined as those occurring after the first HIV-related test. For patients with multiple primary cancers, we presented the first incident cancers, respectively. In addition, we described the characteristics of patients by each cancer of interest. We presented summary measures as medians and interquartile ranges for age at baseline, first CD4 cell count and person-years (pyears) of follow-up. We calculated the crude incidence rate for each cancer of interest across the 11-years study period per 100 000 pyears. We considered the date of first HIV-related laboratory records as the date of entry into the cohort (baseline). We defined the exit date from the cohort as either the date of cancer diagnosis, the date of last HIV-related test plus an additional 180 days or December 31, 2014, which was the closure of the database, whichever came first. In addition, we determined the age specific incidence rate for all cancers of interest.

To determine the factors associated with increased risk of HPV-related cancers and hormone-related cancers in WLHIV, we used Cox proportional hazard models. We specifically explored in univariable analysis the effect of CD4 cell counts, HIV RNA viral loads, baseline age, calendar period, SEP and settlement type on the incidence of cervical cancer and HPV-related cancer other than cervix (vulva and vaginal cancer), as well as breast cancer and hormone-related cancer other than breast cancer (cancer of the ovary and uterus). We excluded placenta cancers from the grouped analysis, as they did not fit the groups mentioned above. Since CD4 cell counts and HIV RNA viral loads in our study were highly correlated ($r = -0.0386$; P value <.001), we fitted separate models, including either CD4 cell counts or HIV RNA viral loads. In the multivariable analysis, the final model selection for cervical and other HPV-related as well as breast and other hormone-related cancers included age, calendar period, SEP and settlement type. CD4 cell counts and HIV RNA viral loads were only included for cervical and other HPV-related cancer. Due to the centralised cancer care model in South Africa[18] and the data linkage process,[10] we stratified all regression models by the province of first HIV-related laboratory record. We used STATA 16.1 for all analyses.

2.4 | Sensitivity analyses

Since data on HIV RNA viral load was largely missing (N = 1 309 908 [38%]), we used multiple imputation with chained equations to determine the values of the missing data assuming that the data were missing at random. We log transformed the CD4 cell counts and HIV RNA viral loads and used linear regression for the imputation of CD4 cell counts. Across the years, the detection limits of HIV RNA viral load tests have been changing. We determined that the detection limits ranged from 0 to 400 copies/ml from 2004 to 2014. However, for individuals with missing data imputed as below the detection limit of

HIV RNA viral load tests, we did not know the exact value of this missing data point. As a result, we used interval regression to impute these data. Our study included patients between the ages of 15 and 100 years, for that reason we used truncated regression to impute missing baseline age and restricted the imputed data to this age range. Therefore, any imputations beyond these limits were excluded systematically. To predict the missing data points we used patients with complete information on baseline age, HIV RNA viral loads, CD4 cell counts, calendar period, SEP and settlement type of first HIV test as well as the cancer type. We used multivariable imputation with chained equations to impute five datasets. We used the imputed dataset to determine risk factors for developing cancer and compared the results to the complete case analysis. Estimates were combined using Rubin's rules which adjusts coefficients and standard errors for variability across datasets.[19] As an additional sensitivity analysis, to assess the impact of subclinical prevalent cancers, we excluded patients who were diagnosed with cancer within the first 6 months and women that had a follow-up time of <6 months from the incidence analysis.

3 | RESULTS

3.1 | Study population

In the study period, 3 447 908 WLHIV had two or more HIV-related laboratory tests done in the public health sector. A total of 11 348 incident and 7612 prevalent hormone-related and HPV-related cancers cases were observed. Table 1 shows the characteristics of the women included in the HIV cohort. The median age at first HIV-related test was 41 years (Interquartile range [IQR]: 34-48) for WLHIV diagnosed with incident cancer and 32 years (IQR: 26-40) for WLHIV not developing cancer. Women with prevalent cancers were older at HIV diagnosis (47 years; IQR: 40-54) compared those with incident or no cancer diagnosis. The proportion of women 50 years and older with prevalent cancer was higher than that of those with incident cancers at 40% and 20%, respectively. The median first CD4 cell count was 269 cells/μl (IQR: 147-433) for WLHIV diagnosed with incident cancer and 306 cells/μl (IQR 172-474) for WLHIV not developing cancer. About 62% (n = 4809) of WLHIV diagnosed with incident cancer had a first HIV RNA viral load <1000 copies/ml, whilst 68% (n = 1 451 347) WLHIV free from cancer had an HIV RNA viral load of <1000 copies/ml. For WLHIV with and without cancer there were more patients diagnosed in high SEP municipalities compared to low SEP municipalities. We observed the same for settlement type with more WLHIV diagnosed in urban municipalities compared to rural municipalities. The median follow-up time was similar in WLHIV diagnosed with (median: 1.83 years; IQR: 0.44-3.93) and without cancer (median: 2.53 years; IQR: 1.17-4.31).

Amongst incident gynaecologic and breast cancer, cervical cancer was the most frequently diagnosis in WLHIV with 7383 cases followed by breast cancer with 2737 cases (Table 2). Placenta cancer was the least common with 52 cases. The median age at cancer diagnosis was highest for uterine cancer (51 years, IQR: 42-58) and lowest for placenta cancers (30 years, IQR: 25-36). The median CD4 cell counts were similar for all incident cancers ranging from 238 to 340 cells/μl whilst majority of WLHIV had a viral load of <1000 copies/ml across all cancers. The median follow-up time ranged from 1.60 pyears (IQR: 0.12-2.89) for placenta cancers to 2.44 pyears (0.67-4.98) for cancer of the vulva.

3.2 | Cancer incidence rates

Over 10 545 000 years of follow-up, the overall incidence rate of any gynaecological and breast cancer was 108/1 00 000 person-years (pyears). The crude incidence rate of cervical cancer ranked first with 70/1 00 000 pyears (95% confidence interval [95% CI]: 68.5-71.7), followed by breast cancer with an incidence of 26/1 00 000 pyears (95% CI: 25.0-26.9). Cancer of the placenta had the lowest incidence rate (0.49/1 00 000 pyears; 95% CI: 0.38-0.65). The age-specific incidence rate for cervical cancer rose from 3/1 00 000 pyears in 15 to 19-year-olds to 245/1 00 000 pyears in WLHIV 60 years and older (Figure 1 and Table S1). We observed a similar pattern for other HPV-related cancers. Breast cancer incidence rate ranged from 1.06/1 00 000 pyears to 120/1 00 000 pyears in the lowest and highest age groups. For other hormone-related cancers, the incidence remained low and stable in WLHIV 15 to 25 years old.

3.3 | Cancer risk factors

3.3.1 | HPV-related cancers

In the univariable and multivariable analyses, the risk of developing cervical and other HPV-related cancer decreased with increasing CD4 cell counts (Figure 2 and Tables 3 and S2). Specifically, compared to WLHIV with CD4 cell counts of <200 cells/μl, WLHIV with CD4 cell counts above 500 cells/μl had a lower risk of developing cervical cancer (Hazard ratio [HR]: 0.82; 95% CI: 0.77-0.88) and other HPV-related cancers (HR:0.62; 95% CI:0.49-0.79). Similarly, WLHIV with HIV RNA viral loads >1000 copies/ml had a higher risk of developing cervical cancer or other HPV-related cancers as compared to those with <1000 copies/ml (HR: 1.32; 95% CI: 1.25-1.40; and 1.34; 95% CI 1.11-1.63, respectively) (Figure 3 and Table S3). Older WLHIV had an increased risk of developing HPV-related cancers as compared to younger WLHIV in the models adjusting for CD4 cell counts or HIV RNA viral loads. In both models, the risk of developing cervical cancer decreased in calendar years that are more recent. In contrast, there was no such evidence for other HPV-related cancers. The risk of being diagnosed with HPV-related cancer was higher in facilities of high SEP compared to facilities in municipalities of low SEP, except for other HPV-related cancers in the model adjusting for HIV-RNA viral loads. There was no evidence of an association between HPV-related cancers risk and settlement type.

TABLE 1 Characteristics of participants by prevalent, incident and no cancer diagnosis in women living with HIV in South Africa.

	Prevalent cancers N = 7612 N (%)	Incident cancers N = 11 348 N (%)	No cancer diagnosis N = 3 436 560 N (%)
Age at first lab record (years)			
15-19	8 (0.10)	28 (0.20)	126 466 (3.9)
20-29	268 (3.50)	1237 (10.9)	1 166 213 (35.6)
30-39	1596 (21.0)	3924 (34.6)	1 142 903 (34.9)
40-49	2626 (34.5)	3639 (32.1)	561 957 (17.2)
50-59	2111 (27.7)	1928 (17.0)	219 348 (6.70)
60-69	777 (10.2)	482 (4.25)	48 426 (1.48)
70+	226 (2.97)	110 (0.97)	9389 (0.29)
Missing			161 858
Median (IQR)	47 (40-54)	41 (34-48)	32 (26-40)
First CD4 cell count recorded (cells/μl)			
≤200	2411 (32.3)	4097 (36.5)	1 021 535 (30.2)
201-350	2009 (26.9)	3094 (27.5)	930 480 (27.5)
351-500	1339 (17.9)	1980 (17.6)	684 006 (20.2)
≥501	1705 (22.8)	2065 (18.4)	748 082 (22.1)
Missing	148	112	52 457
Median (IQR)	298 (163-479)	269 (147-433)	306 (172-474)
First HIV RNA viral load (copies/ml)			
<1000	3214 (70.3)	4809 (61.6)	1 451 347 (68.0)
≥1000	1361 (29.7)	3000 (38.4)	681 881 (32.0)
Missing	3037	3539	1 303 332
Calendar period of first laboratory record			
2004-2006	841 (11.0)	3158 (27.8)	491 273 (14.3)
2007-2010	3254 (42.7)	5491 (48.4)	1 509 644 (43.9)
2011-2014	3517 (46.2)	2699 (23.8)	1 435 643 (41.8)
Facility related municipality characteristics			
Socioeconomic position			
Low	815 (10.7)	944 (8.30)	545 357 (15.9)
Lower-middle	1270 (16.7)	1720 (15.2)	572 936 (16.7)
Upper-middle	1333 (17.5)	2062 (18.2)	583 361 (17.0)
High	4191 (55.1)	6612 (58.3)	1 732 420 (50.4)
Missing	3	10	2486
Settlement type			
Rural	3791 (49.8)	5308 (46.8)	1 855 369 (54)
Urban	3818 (50.2)	6030 (53.2)	1 578 705 (46)
Missing	3	10	2486

3.3.2 | Hormone-related cancers

The strongest predictor for developing hormone-related cancers in WLHIV was age. Older WLHIV had an increased risk of developing hormone-related cancer compared to younger WLHIV, with the effect more pronounced than for HPV-related cancers. There was also some evidence of an increased risk of breast cancer in facilities of high municipal SEP compared to facilities of low municipal SEP. Settlement type was not associated with hormone-related cancers risk. The results for the individual cancers are presented in the supplement (Tables S10-S12).

3.3.3 | Findings from sensitivity analyses

With the multiple imputation analyses, we observed results similar to the complete case analyses across all cancer groups (Tables S7-S9). Likewise, when we restricted the follow-up time to those with

TABLE 2 Characteristics of women living with HIV at first HIV-related test stratified by each female specific cancer.

	N (%)						
	Cervix N = 7383	Breast N = 2737	Vagina N = 143	Vulva N = 465	Uterus N = 302	Ovary N = 173	Placenta N = 52
Patient related characteristics							
Age at first lab record (years)							
15-19	12 (0.20)	4 (0.10)		2 (0.40)	2 (0.7)	3 (1.7)	5 (9.6)
20-29	797 (10.8)	234 (8.50)	19 (13.3)	124 (26.7)	11 (3.6)	31 (17.9)	18 (34.6)
30-39	2676 (36.2)	894 (32.7)	52 (36.4)	189 (40.6)	46 (15.2)	34 (19.7)	19 (36.5)
40-49	2416 (32.7)	925 (33.8)	46 (32.2)	94 (20.2)	79 (26.2)	49 (28.3)	10 (19.2)
50-59	1161 (15.7)	519 (19.0)	21 (14.7)	49 (10.5)	109 (36.1)	43 (24.9)	0
60-69	260 (3.50)	141 (5.20)	5 (3.50)	5 (1.10)	42 (13.9)	13 (7.50)	0
70+	61 (0.80)	20 (0.70)	0	2 (0.40)	13 (4.30)	0	0
Median (IQR)	40 (34-47)	42 (35-49)	40 (32-48)	34 (29-43)	51 (42-58)	43 (33-52)	30 (25-36)
First CD4 cell count recorded (cells/μl)							
≤200	2782 (38.1)	870 (32.1)	57 (39.9)	191 (41.4)	98 (32.8)	62 (36)	14 (27.5)
201-350	1991 (27.2)	765 (28.2)	39 (27.3)	129 (28.0)	86 (28.8)	52 (30.2)	13 (25.5)
351-500	1270 (17.4)	519 (19.1)	28 (19.6)	63 (13.7)	42 (14.0)	27 (15.7)	14 (27.5)
≥501	1266 (17.3)	559 (20.6)	19 (13.3)	78 (16.9)	73 (24.4)	31 (18)	10 (19.6)
Missing	74	24		4	3	1	1
Median (IQR)	263 (141-422)	292 (163.4-465)	248 (141-426.25)	238 (138-386)	280 (165-492)	273 (145-413)	340 (189-468)
First HIV RNA viral load (copies/ml)							
<1000	3029 (60.5)	1247 (63.8)	66 (64.7)	206 (58.9)	134 (65.4)	75 (63.0)	13 (52.0)
≥1000	1977 (39.5)	709 (36.2)	36 (35.3)	144 (41.1)	71 (34.6)	44 (37.0)	12 (48.0)
Missing	2377	781	41	115	97	54	27
Calendar period of first lab record							
2004-2006	2053 (27.8)	809 (29.6)	38 (26.6)	142 (30.5)	64 (21.2)	51 (29.5)	10 (19.2)
2007-2010	3535 (47.9)	1346 (49.2)	61 (42.7)	216 (46.5)	160 (53.0)	87 (50.3)	29 (55.8)
2011-2014	1795 (24.3)	582 (21.3)	44 (30.8)	107 (23)	78 (25.8)	35 (20.2)	13 (25)
Facility related municipality characteristics							
Socioeconomic position							
Low	605 (8.2)	224 (8.20)	14 (9.8)	40 (8.60)	39 (12.9)	10 (5.80)	3 (5.90)
Lower-middle	1186 (16.1)	365 (13.4)	20 (14)	54 (11.6)	49 (16.2)	25 (14.5)	8 (15.7)
Upper-middle	1403 (19.0)	459 (16.8)	20 (14)	80 (17.2)	49 (16.2)	29 (16.8)	10 (19.6)
High	4186 (56.7)	1684 (61.6)	89 (62.2)	290 (62.5)	165 (54.6)	109 (63.0)	30 (58.8)

(Continues)

TABLE 2 (Continued)

	N (%)						
	Cervix N = 7383	Breast N = 2737	Vagina N = 143	Vulva N = 465	Uterus N = 302	Ovary N = 173	Placenta N = 52
Missing	3	5		1		1	11
Settlement type							
Rural	3582 (48.5)	1179 (43.2)	64 (44.8)	199 (42.9)	145 (48.0)	73 (42.2)	24 (47.1)
Urban	3798 (51.5)	1553 (56.8)	79 (55.2)	265 (57.1)	157 (52.0)	100 (57.8)	27 (52.9)
Missing	3	5		1		1	
Median follow-up time (pyears)	1.61 (0.32-3.72)	2.34 (0.86-4.23)	2.17 (0.33-3.85)	2.44 (0.67-4.98)	1.71 (0.28-3.84)	1.63 (0.38-3.70)	1.60 (0.12-2.89)
Crude incidence rate/1 00 000 pyears (95%CI)	70.0 (68.5-71.7)	25.9 (25.0-26.9)	1.35 (1.15-1.59)	4.40 (4.02-4.82)	2.86 (2.55-3.20)	1.64 (1.41-1.90)	0.49 (0.38-0.65)

Abbreviations: 95% CI, 95% confidence interval; IQR, interquartile range.

>6 months follow-up time, we observed results comparable to the complete case analysis (Tables S4 and S5).

4 | DISCUSSION

In this South African nationwide study of gynaecological and breast cancers in WLHIV, we observed the highest incidence rate for cervical cancer followed by cancer of the breast, vulva, uterus, ovary, vagina and placenta. We observed a higher risk of breast, cervical and other HPV-related cancer diagnosis in WLHIV accessing HIV care in high SEP areas compared to women accessing care in areas of low SEP. The risk of developing cervical cancer or another HPV-related cancer increased with decreasing CD4 cell counts and increasing HIV RNA viral loads. Cancer risk in WLHIV increased with older age for all cancer types studied with more pronounced effects for hormone-related cancers.

Our study is the first to explore breast and all gynaecologic cancers and their risk factors in WLHIV at a population level in South Africa. Since the HIV cohort was created using NHLS data, our study had a population coverage of about 80%. It is also the first study to look at the association of municipal SEP of health facilities and risk of breast and all gynaecologic cancers other than cervical cancer in WLHIV in South Africa. Our study had some limitations. Our HIV data might be incomplete with point of care HIV tests largely missing in the NHLS database. We observed a relatively short follow-up time in our cohort. In addition, the NCR estimates in our study were from the pathology-based registry, leading to under ascertainment of cancers that are diagnosed only clinically. Therefore, our incidence rates may under- or overestimate the true burden of cancer. The under- or overestimates may also differ by cancer type, as some cancers are diagnosed more easily than others. A large proportion of participants had missing HIV RNA viral loads, which we accounted for using multiple imputation. Still, we had limited information to predict the missing data, which might result in limitations similar to the complete case analysis. Data on ethnicity, which has been shown to be associated with disparities in cancer risk amongst people living with HIV, was unavailable. However, the assumption would be that most of the women were black as the prevalence of HIV is highest amongst black women in South Africa.[8] We lacked information on other risk factors than age for hormone-related cancers than age such as, obesity and hormonal contraceptive use, which might have resulted in residual confounding thus the large effect of age observed. Data on SEP and settlement type was at municipal level and not at individual level. Therefore, interpretation of findings should be kept at municipal level, as we cannot infer individual risk.

The incidence rates that we observed in WLHIV were lower than that observed in WLHIV in South Africa and Zimbabwe[20-22] but also higher than reported in Malawi.[23] The inconsistencies in the reported incidence rates could have been due to differences in study designs and definitions of time at risk. As explained in the limitations section, we cannot exclude that shortcomings in the estimation of our study numerator and denominator may have led to an underestimation of

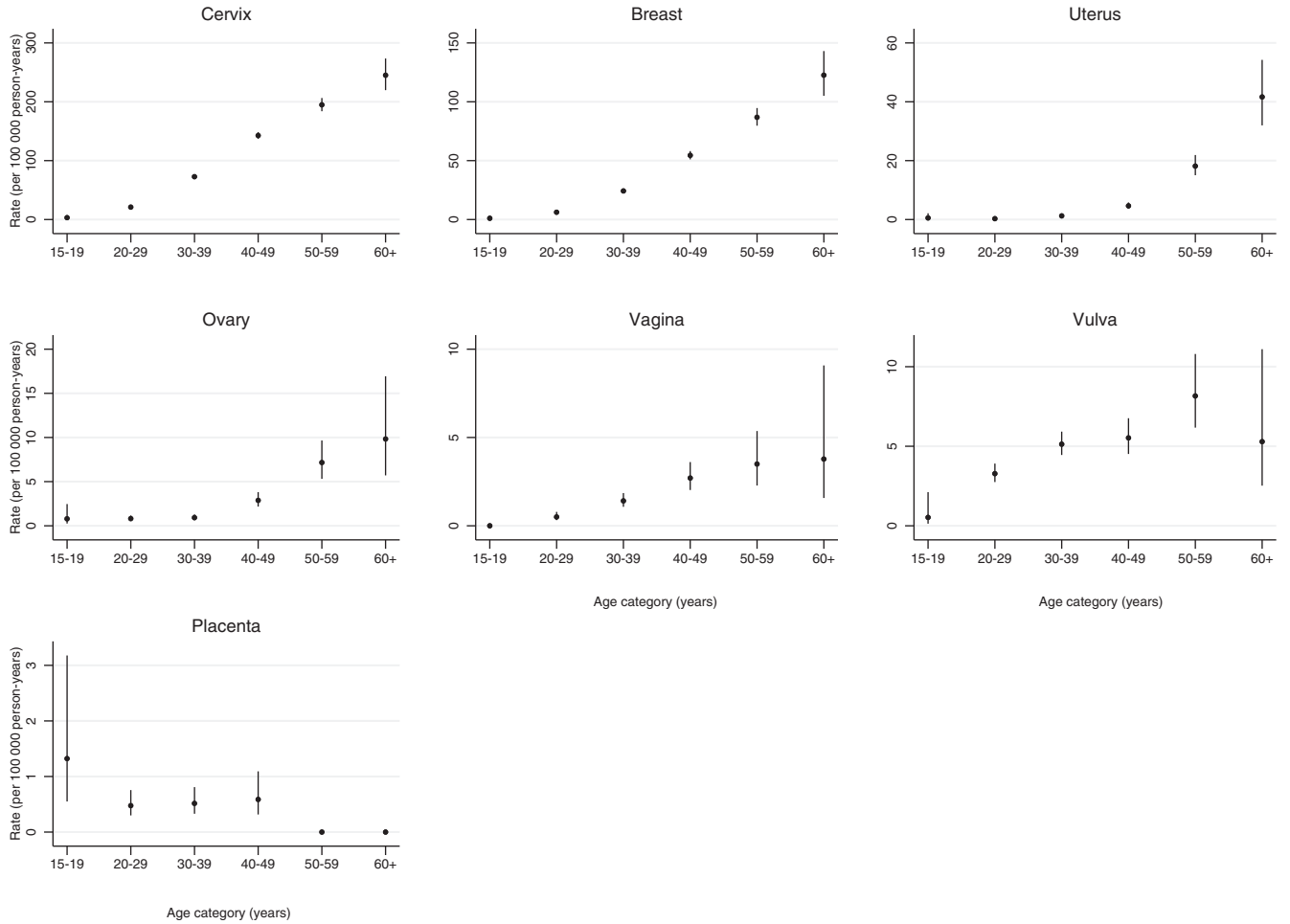

FIGURE 1 Age specific incidence rate/100000 person-years by individual cancer.

the reported cancer incidence rates. In our study, we observed an elevated risk of HPV-related cancers with decreasing CD4 cell counts and high-level HIV RNA viremia. Our results are in line with retrospective studies documenting low median CD4 cell counts at the time of cancer diagnosis for HPV-related cancers including vulvar and cervical cancer, and higher CD4 cell counts in other hormone-related cancers, that is, ovary, uterine cancer.[4] In a multicentre cohort study on WLHIV diagnosed with gynaecologic cancers, high-level viremia was only observed for cervical cancer.[4] The increased incidence of HPV-related cancers in WLHIV has been attributed to HIV-induced immunodeficiency, elevated HPV prevalence and persistence of HPV-infections.[24-27]

Age is an established risk factor for cancer development, and in our study, older ages were associated with a higher risk of all cancers under study with the strongest association observed for other hormone-related cancers. A study including WLHIV in the United States observed that the median age for vulvar, cervical, ovary and uterine cancer was 47, 45, 50 and 53 years, respectively[4] and this is older than the 34, 40 and 43 and 51 years we observed for the same cancers in our cohort of WLHIV. A younger HIV population in South Africa compared to other regions might explain these differences.[28] Another analysis form the SAM study evaluated the association of age and cancer in people living with HIV in South Africa and showed that whilst infection related cancers were more common, infection unrelated cancers were, predominant in HIV patients aged 54 years and older compared to younger people.[29] Few studies have assessed the incidence and age-specific incidence rate of other hormone-related cancers in WLHIV globally and in African settings these data are generally not available for comparison. Of note is the number of prevalent cancers in WLHIV aged 50 and older which even exceeded the incident cancers reported in the same age groups. This corresponds to the national HIV survey results which show that, about 54% of women aged 50 years and older are unaware of their HIV positive status.[8]

The diagnosis of breast, cervical and other HPV-related cancer in our cohort was associated with health facilities in high SEP municipalities. Using area level deprivation, most studies in the general European population have demonstrated an elevated risk of breast cancer and a lower risk of cervical cancer in areas of high SEP compared to areas of low SEP.[30-33] In a previous analysis of the SAM study evaluating the spatiotemporal distribution of cervical cancer in WLHIV across municipalities, an elevated incidence of cervical cancer in high SEP municipalities as well as municipalities with a higher number of health facilities was observed.[34] In our study, the increased risk

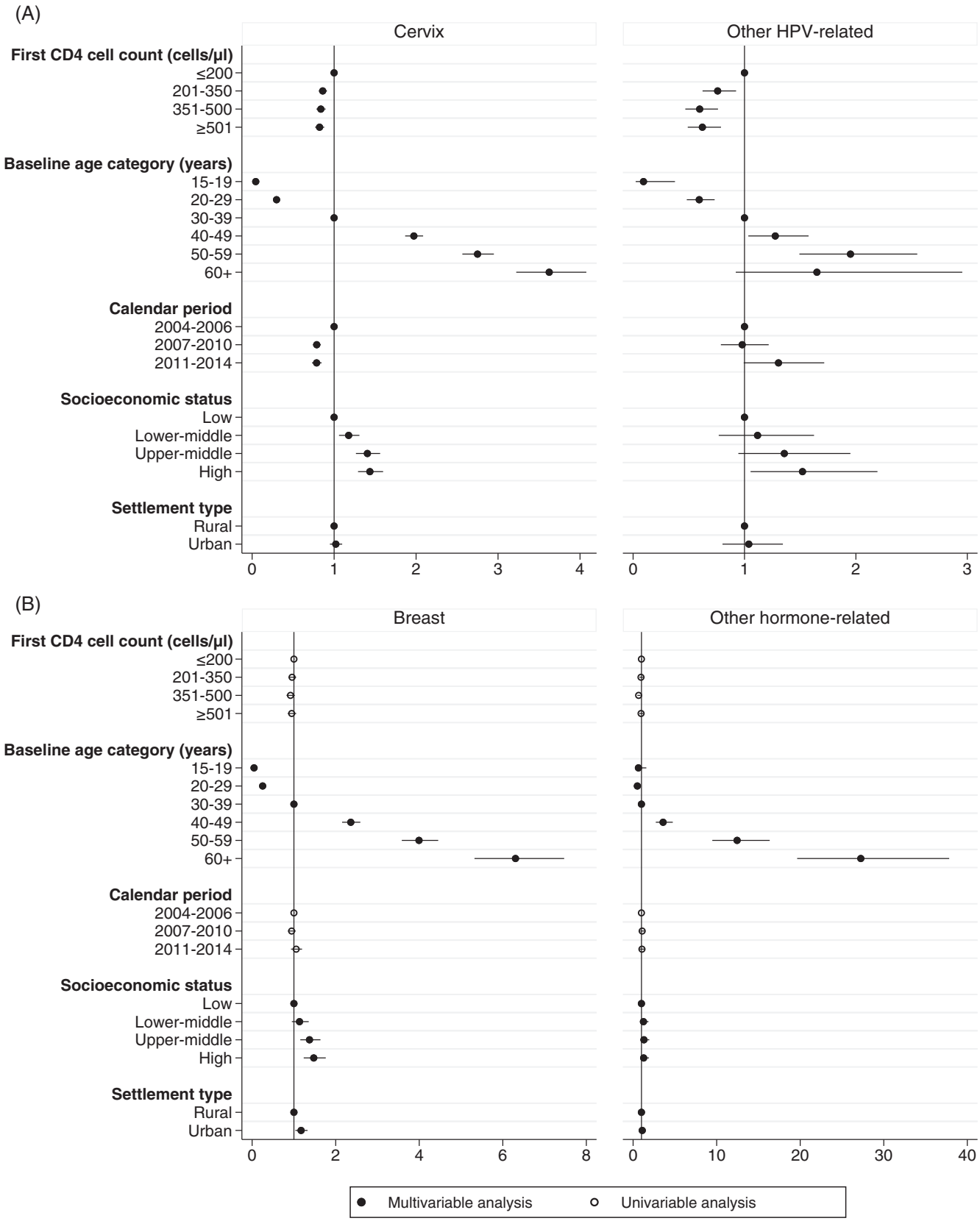

FIGURE 2 Factors associated with gynaecologic and breast cancer in WLHIV: models including CD4 cell count. Cervical cancer and other HPV-related cancer models adjusted for baseline age, calendar period, socio-economic status and settlement type (A). Breast and other hormone-related cancer models adjusting for baseline age, socio-economic status and settlement type (Panel B). Other HPV related = cancer of the vagina and vulva. Other hormone related = cancer of the uterus and ovary. Clear circle represents variables only evaluated in the univariable analysis.

TABLE 3 Univariable analysis of the factors associated with cancer incidence in women living with HIV.

	HPV-related cancer		Hormone-related cancer	
	Cervix HR (95% CI)	Other HR (95% CI)	Breast HR (95% CI)	Other HR (95% CI)
Patient level characteristics				
First CD4 cell count recorded (cells/μl)				
≤200	1	1	1	1
201-350	0.79 (0.74-0.83)	0.73 (0.60-0.88)	0.96 (0.87-1.05)	0.94 (0.75-1.19)
351-500	0.71 (0.66-0.75)	0.55 (0.44-0.71)	0.92 (0.82-1.02)	0.66 (0.50-0.88)
≥501	0.67 (0.63-0.72)	0.56 (0.44-0.71)	0.95 (0.85-1.05)	0.95 (0.74-1.22)
First HIV RNA viral load (copies/ml)				
<1000	1	1	1	1
≥1000	1.25 (1.18-1.32)	1.28 (1.05-1.55)	1.05 (0.96-1.16)	1.04 (0.82-1.31)
Age at first lab record (years)				
15-19	0.05 (0.03-0.08)	0.08 (0.02-0.34)	0.05 (0.02-0.12)	0.64 (0.26-1.58)
20-29	0.29 (0.27-0.32)	0.57 (0.47-0.71)	0.25 (0.22-0.29)	0.51 (0.35-0.74)
30-39	1	1	1	1
40-49	1.98 (1.87-2.09)	1.30 (1.06-1.60)	2.36 (2.15-2.59)	3.58 (2.71-4.74)
50-59	2.71 (2.53-2.91)	1.95 (1.49-2.54)	3.94 (3.54-4.40)	12.4 (9.42-16.3)
60+	3.49 (3.11-3.92)	1.65 (0.92-2.96)	6.14 (5.18-7.27)	26.9 (19.4-37.4)
Calendar period of first lab record				
2004-2006	1	1	1	1
2007-2010	0.86 (0.81-0.91)	1.01 (0.82-1.26)	0.95 (0.86-1.04)	1.09 (0.85-1.39)
2011-2014	0.92 (0.86-0.99)	1.35 (1.03-1.77)	1.05 (0.93-1.19)	1.06 (0.78-1.44)
Facility related municipality characteristics				
Socioeconomic position				
Low	1	1	1	1
Lower-middle	1.16 (1.05-1.29)	1.11 (0.76-1.61)	1.12 (0.94-1.34)	1.18 (0.80-1.74)
Upper-middle	1.41 (1.28-1.56)	1.37 (0.96-1.95)	1.40 (1.19-1.66)	1.23 (0.84-1.80)
High	1.44 (1.30-1.58)	1.58 (1.15-2.17)	1.53 (1.31-1.79)	1.17 (0.82-1.66)
Settlement type				
Rural	1	1	1	1
Urban	1.15 (1.08-1.23)	1.28 (1.03-1.58)	1.33 (1.19-1.47)	1.10 (0.86-1.41)

Abbreviations: CI, confidence interval; HR, hazard ratio; HPV related, HPV-related cancer other than cervix, specifically cancer of the vagina and vulva; Hormone related, cancer of the uterus and ovary.

of HPV-related and breast cancer diagnosis in high compared to low SEP municipalities most likely reflects the centralization of South African cancer care.[35] This subsequently leads to higher laboratory confirmed cancer diagnoses. In addition the high proportion of specialised health practitioners particularly in facilities in high SEP and urban municipalities in the country might result in higher cancer detection rates in municipalities of high SEP.[36] Another study evaluating the effect of life course SEP on breast and cervical cancer screening rates indicated higher screening rates in participants with higher SEP.[37] The increased screening rates and higher access to cancer care in high SEP municipalities can also result in better cancer detection rates in these areas. Similar to other studies in the general population we observed no evidence of an association between municipality level SEP with ovarian and uterine cancers.[32] We did not detect a significant association between rural and urban settlement types and cancer risk. A case control study in India showed an increased risk in cervical cancer in rural areas compared to urban areas.[38] In addition, it has been noted that women from rural areas have less access to information on cancer and health care related services, factors that are associated with increased cancer risk. A study in the American general population also observed that women in rural areas likely had less access to gynaecology oncologists resulting in elevated incidence of gynaecologic cancer.[39]

Cancer surveillance in WLHIV is becoming increasingly important especially in the context of women ageing with HIV as it allows for better understanding of cancer burden in this population including risk factors, prognostic factors as well as treatment options. More studies investigating the epidemiology, prevention, diagnosis and treatment

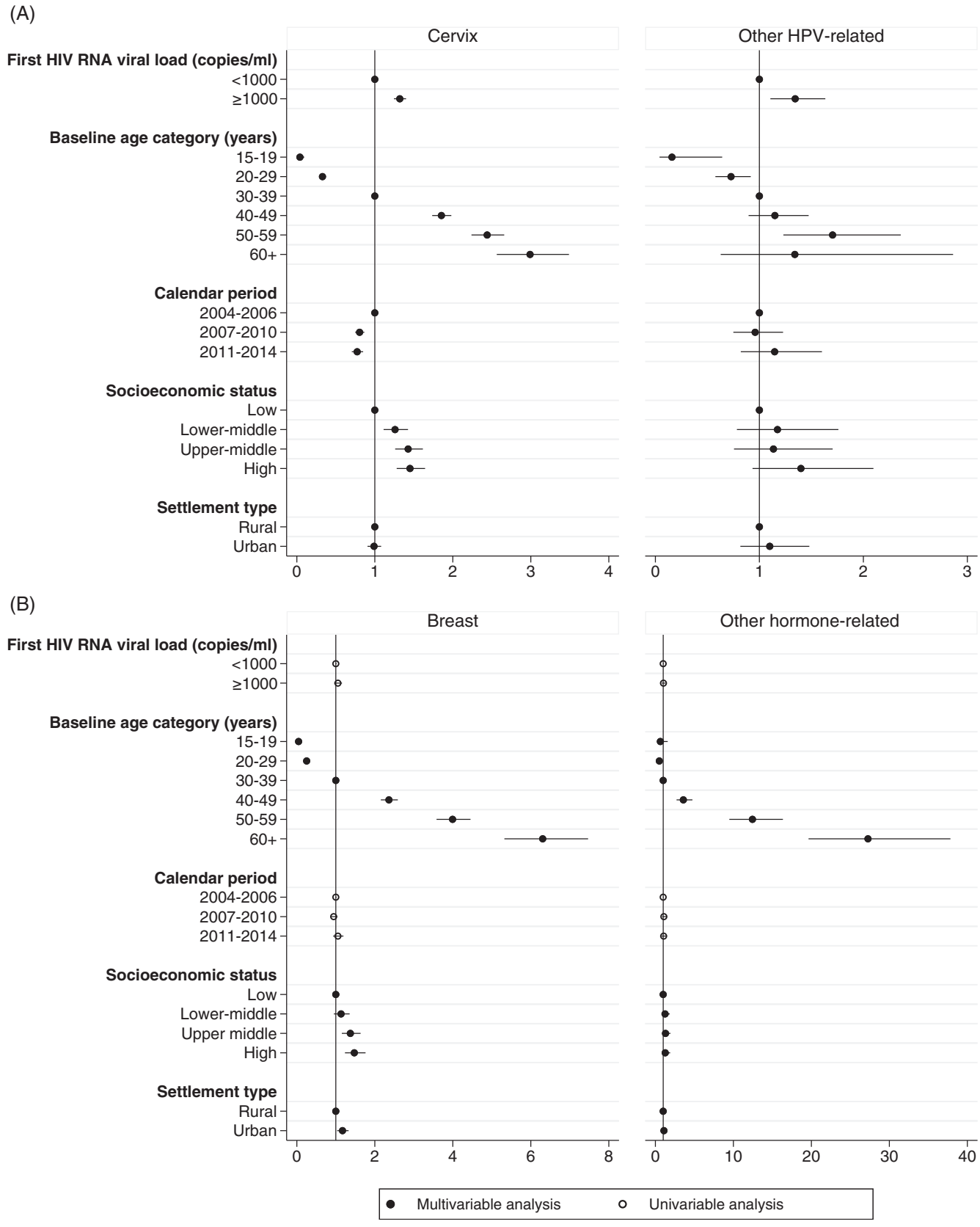

FIGURE 3 Factors associated with gynaecologic and breast cancer in WLHIV: models including HIV RNA viral loads. Cervical cancer and other HPV-related cancer models adjusted for HIV RNA viral load, baseline age, calendar period, socio-economic status and settlement type (A). Breast and other hormone-related cancer models adjusting for baseline age, socio-economic status and settlement type (B). Other HPV related = cancer of the vagina and vulva. Other hormone related cancer = cancer of the uterus and ovary. Clear circles represent variables only evaluated in the univariable analysis. A, HPV-related cancers; B, hormone-related cancers.

of gynaecologic cancer, particularly hormone-related cancers, should be encouraged. Women should continue to be encouraged to go for HIV testing across all age groups. Integration of HIV and other women's health services should still be encouraged and go beyond cervical cancer screening. Strategies such as cancer screening, early detection (where applicable), and diagnostic services should be scaled-up to reach women at high risk and in low SEP areas. Given that cervical and other HPV-related cancers contribute a significant proportion of the cancer burden in WLHIV, effective interventions like HPV-vaccination and cervical screening using HPV tests remain essential components in the prevention and early detection of these cancers.

5 | CONCLUSIONS

In conclusion, low CD4 cell counts and high HIV RNA viral loads increased the risk of developing HPV-related cancers amongst WLHIV. Older age was a risk factor for all cancers under study in WLHIV. HPV-related cancers and breast cancer diagnosis was associated with facilities in high SEP municipalities. Whilst cancer prevention and early detection programmes should consider women ageing with HIV, it remains important to improve the immunologic status of WLHIV and address SEP disparities in cancer burden.

AUTHOR CONTRIBUTIONS

Tafadzwa G. Dhokotera, Maša Davidović, Matthias Egger, Mazvita Muchengeti and Julia Bohlius contributed towards the study design. Tafadzwa G. Dhokotera contributed towards literature search, data analysis and drafting of first version of manuscript. Mazvita Muchengeti contributed towards data acquisition. Victor Olago contributed towards data linkage. All authors contributed towards data interpretation and critical comments on the first and subsequent drafts of the manuscript. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The original data set analyzed in the present article used patient-level data and was provided by the Academic Affairs and Research Office at the National Health Laboratory Service (NHLS), South Africa. Data is available from the NHLS (Contact academic.research@nhls.as.za) for researchers who meet the relevant criteria for access to these data. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

This study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M190594), Johannesburg, South Africa, and the Cantonal Ethics committee (2016-00589) in Bern, Switzerland.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Immunodeficiency and Cancer in 3.5 Million People Living With Human Immunodeficiency Virus (HIV): The South African HIV Cancer Match Study

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I contributed towards the data interpretation and I provided comments on the first and subsequent drafts of the manuscripts.

Clinical Infectious Diseases

MAJOR ARTICLE

Immunodeficiency and Cancer in 3.5 Million People Living With Human Immunodeficiency Virus (HIV): The South African HIV Cancer Match Study

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Background. We analyzed associations between immunodeficiency and cancer incidence in a nationwide cohort of people living with human immunodeficiency virus (HIV; PLWH) in South Africa.

Methods. We used data from the South African HIV Cancer Match Study built on HIV-related laboratory measurements from the National Health Laboratory Services and cancer records from the National Cancer Registry. We evaluated associations between time-updated CD4 cell count and cancer incidence rates using Cox proportional hazards models. We reported adjusted hazard ratios (aHRs) over a grid of CD4 values and estimated the aHR per 100 CD4 cells/μL decrease.

Results. Of 3 532 266 PLWH, 15 078 developed cancer. The most common cancers were cervical cancer (4150 cases), Kaposi sarcoma (2262 cases), and non-Hodgkin lymphoma (1060 cases). The association between lower CD4 cell count and higher cancer incidence rates was strongest for conjunctival cancer (aHR per 100 CD4 cells/μL decrease: 1.46; 95% confidence interval [CI], 1.38–1.54), Kaposi sarcoma (aHR, 1.23; 95% CI, 1.20–1.26), and non-Hodgkin lymphoma (aHR, 1.18; 95% CI, 1.14–1.22). Among infection-unrelated cancers, lower CD4 cell counts were associated with higher incidence rates of esophageal cancer (aHR, 1.06; 95% CI, 1.00–1.11) but not breast, lung, or prostate cancer.

Conclusions. Lower CD4 cell counts were associated with an increased risk of developing various infection-related cancers among PLWH. Reducing HIV-induced immunodeficiency may be a potent cancer-prevention strategy among PLWH in sub-Saharan Africa, a region heavily burdened by cancers attributable to infections.

Keywords. HIV; cancer; immunodeficiency; CD4 cell count; South Africa.

The human immunodeficiency virus (HIV) has been classified as carcinogenic to humans by the International Agency for Research on Cancer [1]. Yet, the mechanisms through which HIV infection increases cancer risk are not fully understood. HIV-induced immunodeficiency and coinfections with oncogenic viruses among people living with HIV (PLWH) are likely to play a key role [2, 3]. Evidence for direct pro-oncogenic effects of HIV, especially in lymphomagenesis, has also emerged [4].

Three infection-related cancers were found to occur particularly frequently among PLWH, namely Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), and cervical cancer. Therefore, these malignancies were included in the case definition of AIDS [5]. However, over time, it has become apparent that PLWH experience higher incidence rates of other non–AIDS-defining cancers, many of which are also infection related [6–8]. For example, PLWH are at increased risk of developing Hodgkin's lymphoma (related to Epstein-Barr virus [EBV]), liver cancer (related to hepatitis B and C virus), stomach cancer (related to *Helicobacter pylori*), and anogenital cancers (related to human papillomavirus [HPV]) compared with the general population [1, 6–8]. Additionally, conjunctival squamous cell carcinoma is an emerging cancer among PLWH in Africa [9].

Immunodeficiency is a strong risk factor for developing KS and NHL [10, 11]. The KS and NHL incidence rates have steeply declined since antiretroviral therapy (ART) became widely available [12]. Advanced immunodeficiency has also been linked to increased rates of certain non–AIDS-defining cancers, such as Hodgkin's lymphoma and liver, lung, and anal cancer among PLWH in the United States or Europe [10, 11]. Studies of non–AIDS-defining cancers in sub-Saharan Africa are often limited by small numbers of incident cases.

We used data from the South African HIV Cancer Match (SAM) Study to assess the association between lower CD4 cell

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counts and the risk of developing various cancer types among 3.5 million PLWH in South Africa.

METHODS

The SAM Study

The SAM study is a nationwide cohort of PLWH in South Africa and has been described in detail elsewhere [13]. Briefly, it is the result of a linkage between HIV-related laboratory records of the National Health Laboratory Services (NHLS) and pathology-based cancer diagnoses from the National Cancer Registry (NCR) for the period 2004–2014. The NHLS is the largest diagnostic pathology service in South Africa and is estimated to cover approximately 80% of the South African population (https://www.nhls.ac.za). Privacy-preserving probabilistic record linkage methods were used to identify NHLS records from the same individual and to link them to cancer diagnoses from the NCR [14]. The study received ethical approval from the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg (M190594), and the Cantonal Ethics committee in Bern (2016–00589).

Inclusion Criteria and Definitions

We included adults aged 18 years and older at cohort entry, with CD4 count measurements on separate days, and who had at least 1 year of follow-up after the date of their first CD4 count. Persons living with HIV entered the cohort at the time of the first HIV-related laboratory test (baseline). We excluded PLWH with missing information on sex or age. Individuals who were diagnosed with cancer before cohort entry were excluded from the analysis of that cancer.

We used the International Classification of Diseases, 10th revision (ICD-10), diagnoses to identify cancer types. We categorized cancers into infection-related and infection-unrelated cancers, including breast cancer (C50), colorectal cancer (C18–C20), cancer of the connective and soft tissue (C49), lung cancer (C34), melanoma of the skin (C43), esophageal cancer (C15), and prostate cancer (C61). Infection-related cancers were further classified according to the infectious agent they are typically associated with (Table 1) [8]. Of note, we categorized conjunctival cancer as infection related because HIV infection is an established risk factor [15]; however, to date, an association with other oncogenic viruses remains unclear. We excluded basal cell carcinoma (C44.0) and squamous cell carcinoma of the skin (C44.1) from all analyses.

Statistical Analysis

We produced descriptive statistics for PLWH with and without cancer. Age and calendar year were assessed at baseline. We defined time-at-risk as starting 1 year after the date of a patient's first CD4 measurement. We right-censored patients 6 months after their last HIV-related laboratory measurement, at the database closing date (1 January 2015) or at the first diagnosis date of the cancer(s) under consideration, whichever came first. Thus, any patient with less than 1 year from the date of their first CD4 measurement to their right-censoring date was not included in the analysis. We analyzed associations between immunodeficiency (as indexed by time-updated CD4 count) and cancer incidence using proportional hazards (Cox) models separately for each cancer type/group. We time-updated CD4 counts at each measurement, carrying the value forward to the following CD4 measurement or censoring, whichever came first. We lagged the CD4 values by 1 year to minimize the risk of our results being affected by reverse causality—that is, we modeled cancer incidence as a function of the CD4 count from 1 year before. We modeled time-updated CD4 count as a continuous variable and produced adjusted hazard ratio (aHR) curves with 95% confidence intervals (CIs) over a grid of CD4 values, for a reference of 200 cells/μL. We modeled the relationship between CD4 count and the log-hazard using penalized spline bases with 3 degrees of freedom [16]. All models were adjusted for sex, age (continuous variable with penalized splines), calendar year (time-updated, categorical: 2004–2007, 2008–2011, 2012–2014), and comorbidity (yes/no, time-updated) from cancers not part of the outcome of interest. The calendar period categories were chosen to represent the changes in South African ART guidelines. In an additional analysis, we compared the relative strength of the CD4–cancer association across different cancers by estimating the aHR per 100 CD4 cells/μL decrease, assuming a linear relationship between CD4 count and the log-hazard. We performed this analysis including both sexes, and separately for men and women. We tested for interactions between

Table 1. Categorization of Infection-Related Cancers

Infection	Cancer	ICD-10 Codes
AIDS-defining cancers		
Human papillomavirus	Cervical	C53
Human herpesvirus 8	Kaposi sarcoma	C46
Epstein-Barr virus	Non-Hodgkin lymphoma	C82-C85
Non–AIDS-defining cancers		
Human papillomavirus	Anal	C21
	Head and neck	Various[a]
	Penile	C60
	Vaginal	C52
	Vulvar	C51
Epstein-Barr virus	Hodgkin's lymphoma	C81
	Nasopharyngeal	C11
HIV[b]	Conjunctival	C69.0
Hepatitis B and C	Liver and bile duct	C22–24
Helicobacter pylori	Stomach	C16
Schistosomiasis	Bladder	C66, C67

Abbreviations: HIV, human immunodeficiency virus; ICD-10, International Classification of Diseases, 10th revision.

[a]Base of tongue (C01), lingual tonsil (C02.4), palatine tonsil (C09.0–09.9), oropharynx (C10.2–10.9), pharynx NOS (C14.0), Waldeyer's ring (C14.2).

[b]HIV infection is an established risk factor for conjunctival cancer but an association with other oncogenic viruses remains controversial.

sex and 100 CD4 count decrease. We assessed the Cox proportional hazards assumption using Schoenfeld residuals. We used the Akaike information criterion (AIC) to compare the model with penalized splines with the model without (ie, the linear model). All analyses were done in Stata 15 (StataCorp LLC, College Station, TX) and R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Cancer Cases and Patient Characteristics

The SAM cohort provided data on 13 608 064 PLWH, of whom 3 532 266 were included in the overall cancer analysis (Supplementary Figure 1). A total of 27 954 adults were excluded from the analysis due to a prevalent cancer diagnosis (Supplementary Table 1). Among the included PLWH, 15 078 developed incident cancer over 9 108 565 person-years. The median time-at-risk was 2.1 years (interquartile range [IQR], .9–3.6 years) and the median number of CD4 measurements was 3 (IQR, 2–5). Among infection-related cancers, the most common types were cervical cancer (4150 cases), KS (2262 cases), and NHL (1060 cases). Non–AIDS-defining infection-related cancers were less common: there were 692 cases of non–AIDS-defining HPV-related cancers, 604 cases of conjunctival cancers, 288 cases of non–AIDS-defining EBV-related cancers, 164 cases of stomach cancers, 122 cases of bladder cancers, and 94 cases of liver and bile duct cancer.

There were 5182 patients diagnosed with an infection-unrelated cancer. The most common infection-unrelated cancer was breast cancer (1873 cases). There were 440 men diagnosed with prostate cancer. Lung cancer (415 cases), colorectal cancer (384 cases), esophageal cancer (370 cases), melanoma of the skin (151 cases), and connective and soft tissue tumors (107 cases) were less common. Excluding these 7 cancer types, there were 1537 patients diagnosed with other infection-unrelated cancers.

Tables 2 and 3 show the baseline characteristics of included PLWH, stratified by cancer type. Less than one-third of the total study population were male (28.6%). Still, most patients with stomach, bladder, lung, and esophageal cancer were male. The baseline median age was generally higher among PLWH with cancer compared with those remaining free of cancer, and ranged from 32.5 years for KS to 55.6 years for prostate cancer compared to 33.7 years in PLWH without cancer. The median CD4 count at baseline was lower in PLWH who developed cancer than those who did not, and ranged from 179 cells/μL in PLWH with conjunctival cancer to 291 cells/μL in PLWH with breast cancer compared to 292 cells/μL in PLWH who were free of cancer. A summary of age and calendar year at cancer diagnosis is shown in Supplementary Tables 2 and 3.

Immunodeficiency and Cancer Incidence

Across all cancers, the penalized spline approach yielded lower or similar AIC values compared with linear models, indicating better fit to the data (Supplementary Table 4). Thus, we chose this approach for our primary analysis.

From visual inspection of results, lower CD4 counts were associated with higher incidence rates of the 3 AIDS-defining cancers (Figure 1), the non–AIDS-defining HPV-related cancers, and conjunctival cancer (Figure 2), but not with higher rates of liver, stomach, or bladder cancer. There was no evidence of an association between lower CD4 counts and higher incidence of non–AIDS-defining EBV-related cancers (Hodgkin's lymphoma and nasopharyngeal cancer). Among infection-unrelated cancers, we found an association between lower CD4 counts and higher incidence of connective and soft tissue cancer (Figure 3). There was also limited evidence of an association with esophageal cancer and melanoma of the skin.

When assuming a linear relationship between CD4 count and the log-hazard, we found that, among infection-related cancers, the association with CD4 count (aHR per 100 CD4 cells/μL decrease) was strongest for conjunctival cancer, followed by KS and NHL (Figure 4). Moreover, there was evidence for a weak protective effect of a lower CD4 count against stomach cancer (aHR per 100 CD4 cells/μL decrease, .92; 95% CI, .87–.98). Among infection-unrelated cancers, the association between a lower CD4 count and cancer incidence was strongest for melanoma of the skin and esophageal cancer. Sex modified the association between CD4 count and cancer incidence for NHL (P = .006) and KS (P = .005), with the association being more substantial in women than men (Supplementary Figure 2).

DISCUSSION

Advanced immunodeficiency is associated with an increased risk of developing AIDS-defining cancers and various non–AIDS-defining infection-related cancers among a nationwide cohort of PLWH in South Africa. The association between lower CD4 counts and higher cancer incidence rates was strong for conjunctival cancer, KS, NHL, and cervical and other HPV-related cancers. We did not find an association between lower CD4 counts and higher rates of cancers related to nonviral infections (ie, stomach [*H. pylori*] and bladder cancer [schistosomiasis]) and common infection-unrelated cancers including breast, lung, and prostate cancer. The association between lower CD4 counts and cancer incidence tended to be stronger in women than men for KS and NHL.

Since the start of the HIV epidemic, many studies have explored the relationship between immunodeficiency and the incidence of infection-related cancers. In line with these, we found a clear association between lower CD4 counts and increased rates of AIDS-defining cancers—that is, KS [10, 11, 17, 18], NHL [10, 11, 19, 20], and cervical cancer [10, 21]. We and

Table 2. Patient Characteristics at the Baseline Test, Stratified by the Type of Diagnosed Cancer and Infection Group

	AIDS-Defining Cancers			Non–AIDS-Defining Cancers							
	Kaposi Sarcoma	Cervical Cancer	Non-Hodgkin Lymphoma	HPV Related[a]	Epstein-Barr Virus Related[b]	Conjunctival Cancer	Liver and Bile Duct Cancer	Stomach Cancer	Bladder Cancer	Infection Unrelated (See Table 3)	Free of Cancer
n	2262	4150	1060	692	288	604	94	164	112	5182	3 517 188
Female	1256 (55.5)	4150 (100.0)	621 (58.6)	487 (70.4)	152 (52.8)	402 (66.6)	47 (50.0)	77 (47.0)	49 (43.8)	3381 (65.2)	2 509 847 (71.4)
Median [IQR] age, years	32.51 [27.37, 38.52]	38.62 [32.73, 45.77]	36.19 [30.25, 42.96]	36.64 [30.63, 45.10]	33.56 [28.04, 39.27]	35.14 [30.47, 40.80]	44.26 [35.02, 51.36]	45.04 [37.99, 53.86]	50.15 [41.24, 57.21]	44.79 [36.16, 52.68]	33.65 [27.55, 41.17]
Calendar period											
2004–2007	1116 (49.3)	1932 (46.6)	511 (48.2)	313 (45.2)	150 (52.1)	280 (46.4)	42 (44.7)	68 (41.5)	46 (41.1)	2388 (46.1)	744 684 (21.2)
2008–2011	1025 (45.3)	1988 (47.9)	491 (46.3)	330 (47.7)	122 (42.4)	287 (47.5)	49 (52.1)	85 (51.8)	57 (50.9)	2491 (48.1)	1 999 166 (56.8)
2012–2014	121 (5.3)	230 (5.5)	58 (5.5)	49 (7.1)	16 (5.6)	37 (6.1)	3 (3.2)	11 (6.7)	9 (8.0)	303 (5.8)	773 338 (22.0)
Median [IQR] CD4 cell count (cells/μL)	256 [137, 389]	263 [139, 420]	221 [112, 355]	200 [105, 348]	253 [150, 422]	179 [87, 302]	219 [128, 380]	263 [155, 464]	289 [151, 425]	264 [139, 422]	292 [164, 453]
CD4 cell count (cells/μL)											
<50	168 (7.4)	267 (6.4)	81 (7.6)	58 (8.4)	15 (5.2)	60 (9.9)	10 (10.6)	16 (9.8)	8 (7.1)	327 (6.3)	198 893 (5.7)
50–99	184 (8.1)	336 (8.1)	121 (11.4)	84 (12.1)	23 (8.0)	94 (15.6)	4 (4.3)	10 (6.1)	5 (4.5)	412 (8.0)	237 854 (6.8)
100–199	386 (17.1)	740 (17.8)	226 (21.3)	156 (22.5)	50 (17.4)	136 (22.5)	22 (23.4)	25 (15.2)	22 (19.6)	961 (18.5)	585 063 (16.6)
200–349	633 (28.0)	1011 (24.4)	258 (24.3)	150 (21.7)	73 (25.3)	143 (23.7)	24 (25.5)	42 (25.6)	27 (24.1)	1257 (24.3)	906 471 (25.8)
350–499	355 (15.7)	630 (15.2)	134 (12.6)	81 (11.7)	45 (15.6)	61 (10.1)	12 (12.8)	20 (12.2)	20 (17.9)	788 (15.2)	631 328 (17.9)
500–699	178 (7.9)	400 (9.6)	67 (6.3)	39 (5.6)	30 (10.4)	28 (4.6)	12 (12.8)	23 (14.0)	12 (10.7)	489 (9.4)	409 079 (11.6)
≥700	79 (3.5)	208 (5.0)	40 (3.8)	28 (4.0)	12 (4.2)	9 (1.5)	1 (1.1)	9 (5.5)	4 (3.6)	281 (5.4)	227 228 (6.5)
Missing	279 (12.3)	558 (13.4)	133 (12.5)	96 (13.9)	40 (13.9)	73 (12.1)	9 (9.6)	19 (11.6)	14 (12.5)	667 (12.9)	321 272 (9.1)

Data are presented as n or n (%) unless otherwise indicated.
Abbreviations: HPV, human papillomavirus; IQR, interquartile range.
[a]Anal, head and neck, penile, vaginal, vulvar cancer.
[b]Hodgkin's lymphoma, nasopharyngeal cancer.

Table 3. Patient Characteristics at the Baseline Test, Stratified by Infection-Unrelated Cancer Diagnosis

	Breast Cancer	Colorectal Cancer	Connective Tissue Cancer	Lung Cancer	Melanoma	Esophageal Cancer	Prostate Cancer	Other Infection-Unrelated Cancers[a]
n	1873	384	107	415	151	370	440	1537
Female	1850 (98.8)	223 (58.1)	59 (55.1)	117 (28.2)	89 (58.9)	166 (44.9)	0 (0.0)	923 (60.1)
Median [IQR] age, years	41.10 [34.18, 48.61]	45.18 [36.16, 53.18]	39.01 [31.22, 48.80]	49.19 [43.56, 55.11]	45.45 [37.55, 53.37]	48.99 [42.59, 55.13]	55.58 [50.46, 60.26]	43.53 [34.39, 51.70]
Calendar period								
2004–2007	896 (47.8)	159 (41.4)	55 (51.4)	183 (44.1)	67 (44.4)	175 (47.3)	173 (39.3)	726 (47.2)
2008–2011	886 (47.3)	194 (50.5)	47 (43.9)	198 (47.7)	77 (51.0)	173 (46.8)	235 (53.4)	721 (46.9)
2012–2014	91 (4.9)	31 (8.1)	5 (4.7)	34 (8.2)	7 (4.6)	22 (5.9)	32 (7.3)	90 (5.9)
Median [IQR] CD4 cell count (cells/μL)	291 [165, 452]	259 [155, 385]	248 [105, 430]	238 [124, 405]	233 [133, 374]	244 [121, 387]	244 [129, 401]	251 [131, 410]
CD4 cell count (cells/μL)								
<50	115 (6.1)	24 (6.2)	8 (7.5)	27 (6.5)	12 (7.9)	19 (5.1)	27 (6.1)	102 (6.6)
50–99	118 (6.3)	19 (4.9)	14 (13.1)	36 (8.7)	12 (7.9)	43 (11.6)	39 (8.9)	137 (8.9)
100–199	287 (15.3)	75 (19.5)	21 (19.6)	88 (21.2)	32 (21.2)	73 (19.7)	84 (19.1)	316 (20.6)
200–349	483 (25.8)	111 (28.9)	18 (16.8)	100 (24.1)	37 (24.5)	90 (24.3)	104 (23.6)	345 (22.4)
350–499	323 (17.2)	56 (14.6)	15 (14.0)	52 (12.5)	20 (13.2)	50 (13.5)	64 (14.5)	215 (14.0)
500–699	187 (10.0)	34 (8.9)	11 (10.3)	37 (8.9)	9 (6.0)	34 (9.2)	42 (9.5)	147 (9.6)
≥700	124 (6.6)	10 (2.6)	7 (6.5)	23 (5.5)	10 (6.6)	11 (3.0)	20 (4.5)	81 (5.3)
Missing	236 (12.6)	55 (14.3)	13 (12.1)	52 (12.5)	19 (12.6)	50 (13.5)	60 (13.6)	194 (12.6)

Data are presented as n or n (%) unless otherwise indicated.
Abbreviation: IQR, interquartile range.
[a]Includes all infection-unrelated cancers not shown in the other columns.

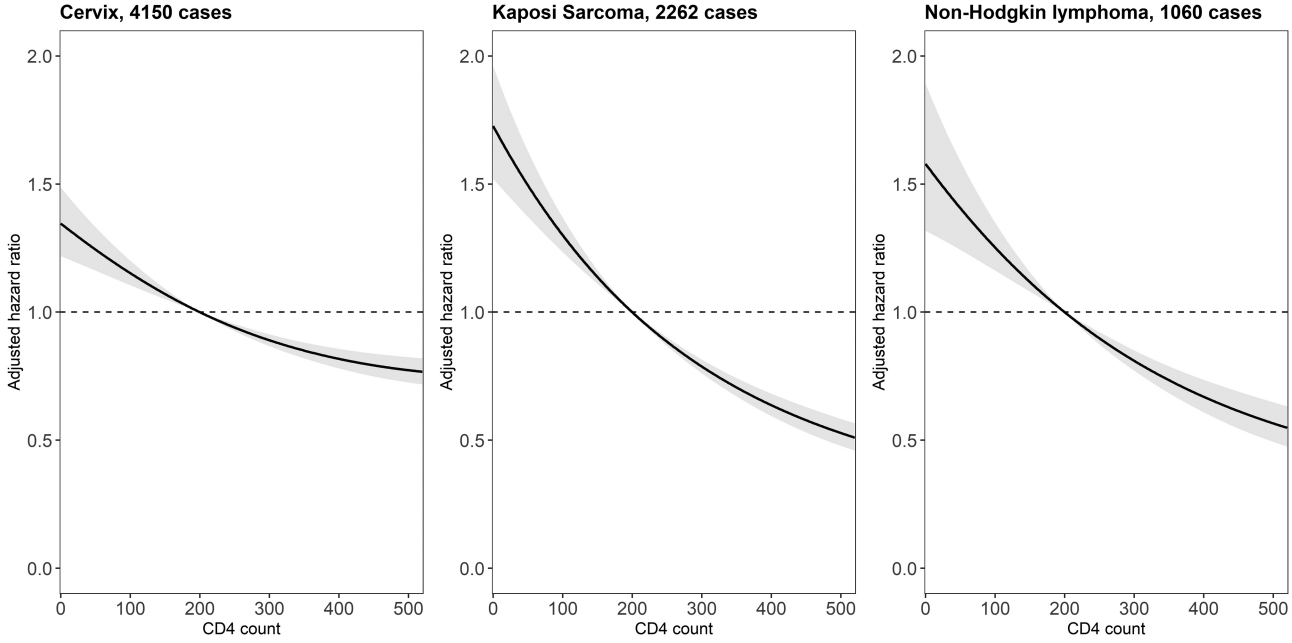

Figure 1. Adjusted hazard ratios (solid lines) with 95% confidence intervals (gray area) for the incidence of AIDS-defining cancers, comparing a grid of CD4 cell counts with the reference value of 200 cells/μL. The models are adjusted for sex, age, calendar year, and diagnosis of other cancers.

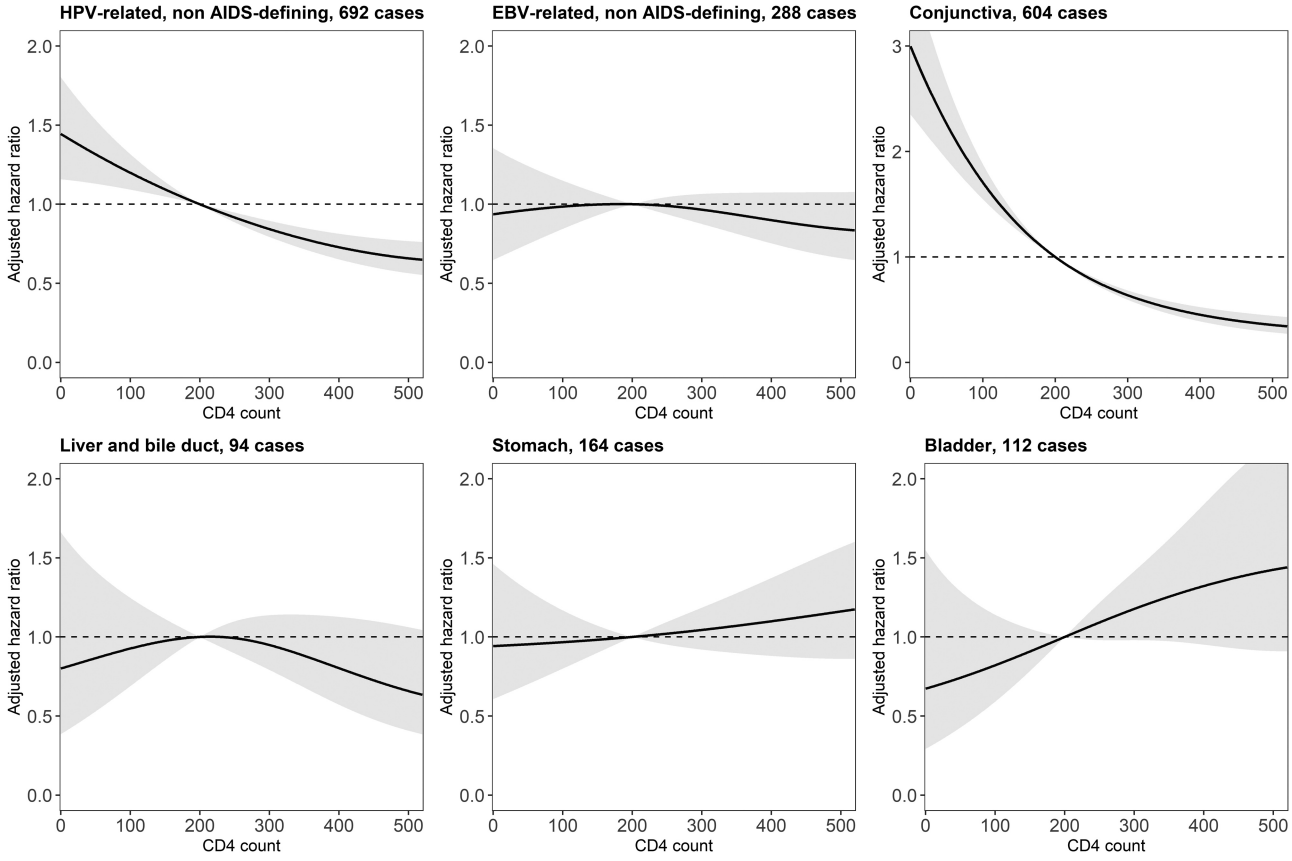

Figure 2. Adjusted hazard ratios (solid lines) with 95% confidence intervals (gray area) for the incidence of infection-related, non–AIDS-defining cancers, comparing a grid of CD4 cell counts with the reference value of 200 cells/μL. The models are adjusted for sex, age, calendar year, and diagnosis of other cancers. Abbreviations: EBV, Epstein-Barr virus; HPV, human papillomavirus.

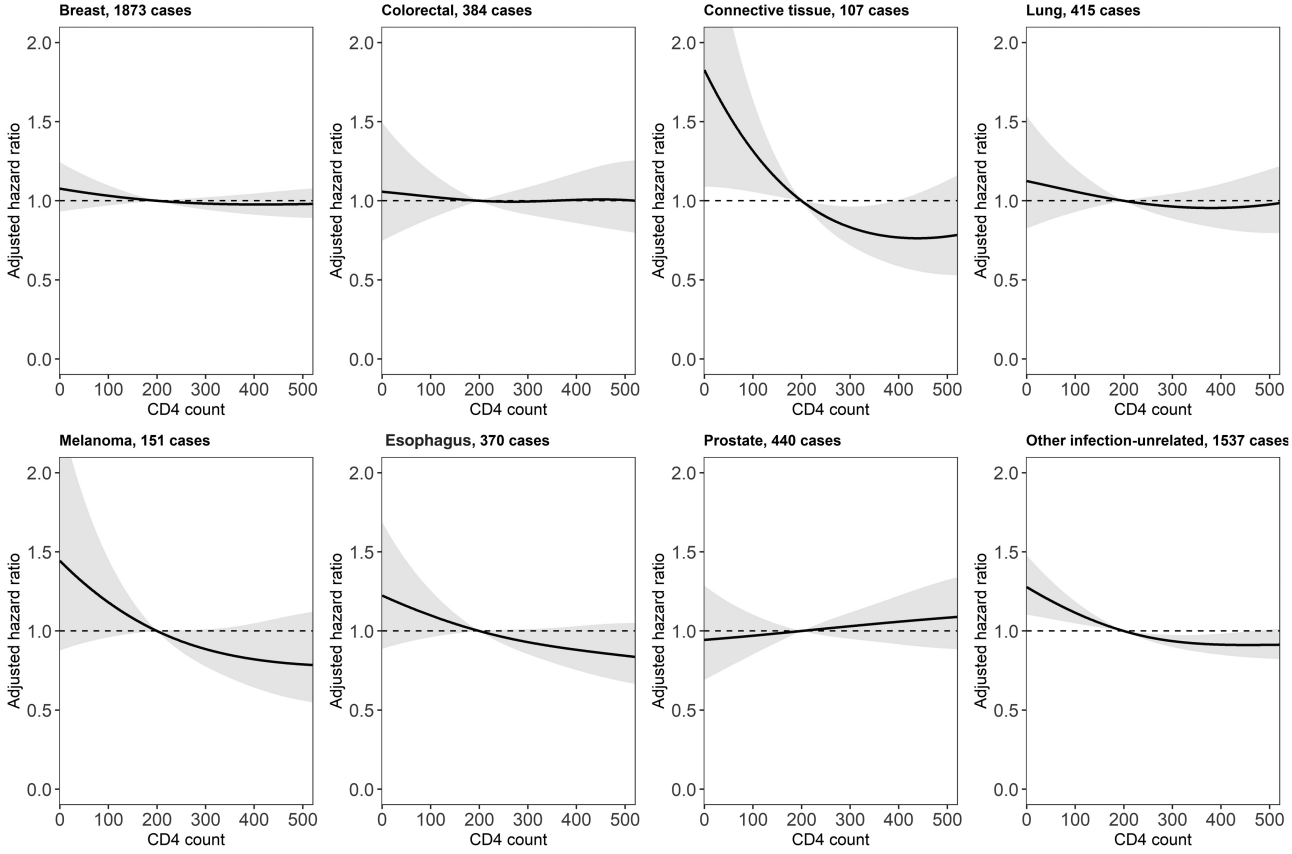

Figure 3. Adjusted hazard ratios (solid lines) with 95% confidence intervals (gray area) for the incidence of infection-unrelated cancers, comparing a grid of CD4 cell counts with the reference value of 200 cells/μL. The models are adjusted for sex, age, calendar year, and diagnosis of other cancers.

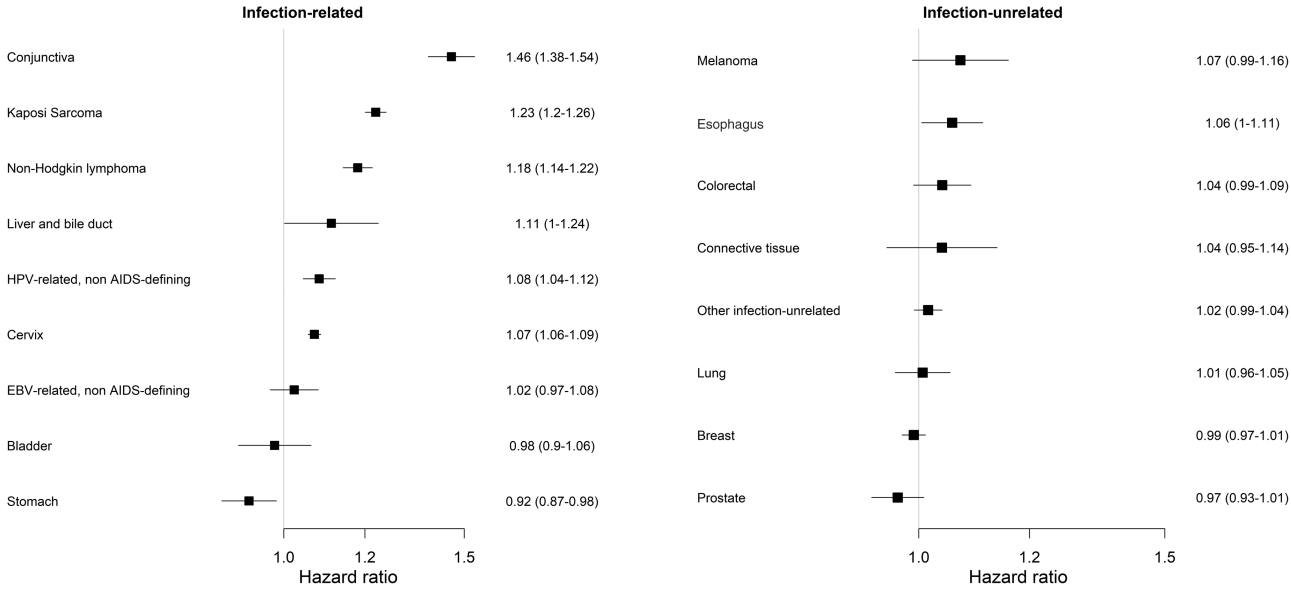

Figure 4. Adjusted hazard ratios for cancer incidence with associated 95% confidence intervals, per 100 cells/μL decrease in CD4 cell count. The models assumed a linear relationship between CD4 cell count and the log-hazard of the cancer, while adjusting for sex, age, calendar year, and diagnosis of other cancers. The cancers are ranked in decreasing order of their adjusted hazard ratios. Abbreviations: EBV, Epstein-Barr virus; HPV, human papillomavirus.

others [10, 11, 22, 23] also observed higher incidence rates of non–AIDS-defining HPV-related cancers such as anal [10, 22], vaginal/vulvar [24], and head and neck squamous cell carcinoma [23] at lower CD4 counts. In our study, we assessed time-updated CD4 counts lagged by 1 year, whereas others identified nadir and cumulative CD4 count as well as CD4 count lagged by several years to be stronger predictors for the risk of developing HPV-related cancers [10, 22, 23]. Immunodeficiency may promote HPV-related carcinogenesis early on by increasing the risk of HPV acquisition and reducing HPV clearance [25]. Our findings only partially confirm an increased liver cancer risk in PLWH with advanced immunodeficiency [10, 11, 26]. Conjunctival cancer is particularly common in Africa and has been linked to ultraviolet radiation and HIV infection [9]. Our results corroborate an important role of immunodeficiency in the development of this cancer. Studies from the United States and Europe identified a clear association between lower recent CD4 counts and high Hodgkin's lymphoma incidence rates [10, 11, 27]. However, we did not find such a trend for EBV-related non–AIDS-defining cancers (Hodgkin's lymphoma and nasopharyngeal cancer). Misdiagnosis of HIV-associated lymphomas as tuberculosis (TB) is common in resource-limited settings with high TB prevalence [28], and this may have distorted the estimated association between immunodeficiency and Hodgkin's lymphoma risk. Of note, the association between CD4 counts and NHL risk in our study was also weaker than what has been described for North America and Europe [10, 11, 19]. Literature on the link between immunodeficiency and the risk of bladder and stomach cancers is scarce. An American study found a higher risk of developing non-cardia stomach cancer among PLWH with nadir CD4 counts of 200 cells/μL or less versus more than 200 cells/μL [29]. We did not find an association between lower CD4 counts and either bladder or stomach cancer incidence.

The association of lower CD4 counts with a KS and NHL risk was stronger among women than men. Most studies to date have not assessed whether the association between immunodeficiency and cancer risk is modified by sex. However, sex differences in cancer susceptibility have been reported consistently, with most cancers occurring more frequently in men [30]. Sex differences in immune surveillance, with women generally mounting stronger immune responses, may contribute to differences in cancer susceptibility between male and female PLWH [31].

Few studies have assessed the association between HIV-induced immunodeficiency and infection-unrelated cancers, and data from Africa are generally not available. In the United States, both breast and prostate cancer occur less frequently among PLWH than in the general population [32, 33], with prostate cancer risk being reduced among men with lower CD4 counts at AIDS diagnosis [34]. However, we did not find an association between lower CD4 counts and either prostate or breast cancer incidence. In our study, there was some evidence for higher incidence rates at lower CD4 counts for esophageal cancer as well as connective and soft tissue tumors. One study also found a higher risk of esophageal squamous cell carcinoma among PLWH with lower nadir CD4, but the uncertainty was considerable [29]. The association between lower CD4 counts and the risk of connective and soft tissue tumors is in line with case reports suggesting an etiological role of EBV in the development of leiomyosarcomas and leiomyomas [35]. However, it could also be a spurious finding if some KS cases were misclassified as other soft tissue sarcomas. For malignant melanoma of the skin, we found a weak association with lower CD4 counts, but previous studies showed conflicting results [11, 36]. The observation that some cancers currently categorized as infection-unrelated showed an association with lower CD4 counts could indicate that an unknown infectious cause may contribute to the development of these cancers.

This is the first large-scale study to explore associations between lower CD4 cell counts and various cancer types in sub-Saharan Africa. Our analysis included CD4 trajectories of 3.5 million PLWH over 9 million person-years. Our study has several limitations. Given that our cohort study was based on routine data, CD4 cell count measurements did not necessarily occur at regular intervals and we did not have access to ART data. However, we adjusted for calendar period, with breakpoints chosen to match changes in South African ART guidelines. Information on cancer risk factors such as coinfections with other oncogenic viruses, lifestyle factors, or socioeconomic status was also unavailable. The database closing date was 1 January 2015, but we do not expect immunodeficiency to influence cancer risk differently over time. The SAM study did not include mortality or emigration data. Thus, we censored patients 6 months after the last laboratory measurement. While this limits the amount of follow-up data in our study, we do not expect it to have biased our results. CD4 count is a commonly studied biomarker. Still, CD8 count, CD4-to-CD8 ratio, or RNA viral load are also important biomarkers for some cancers [10, 37, 38]. The NHLS does not routinely assess CD8 counts, and RNA viral loads were not reported frequently enough to create reliable trajectories.

Close to 30% of cancers in sub-Saharan Africa are infection related [15]. Among PLWH, the proportion of cancers attributable to infections is particularly high, with a proportion of 40% estimated in the United States [8]. In sub-Saharan Africa, the proportion of infection-related cancers among PLWH is likely to be even higher. Reducing immunodeficiency through early detection of HIV and effective ART has been key in decreasing KS and NHL incidence among PLWH worldwide [12, 39], and evidence is accumulating that timely initiation of ART might reduce the risk of developing cervical and anal cancers [40, 41]. However, it is less clear whether reducing HIV-induced immunodeficiency has a preventive effect on other cancers. We have

shown that lower CD4 counts are associated with higher rates of various infection-related and infection-unrelated cancers among PLWH in South Africa. Therefore, preventing HIV-induced immunodeficiency may be an important strategy to reduce the disproportionate cancer burden among PLWH in sub-Saharan Africa. As the effect of immunodeficiency on carcinogenesis varies by cancer types, in-depth cancer-specific analyses are required. The SAM study, with its nationwide cohort of PLWH, provides an ideal platform for such analyses.

In conclusion, lower CD4 counts are associated with an increased risk of developing various infection-related cancers among PLWH. Reducing HIV-induced immunodeficiency may be a potent cancer-prevention strategy among PLWH in sub-Saharan Africa, a region heavily burdened by cancers attributable to infections.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. Calculations were performed on UBELIX (http://www.id.unibe.ch/hpc), the high performance computing cluster at the University of Bern.

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Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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10.2. Non-Peer-Reviewed Publications

Facility-based indicators to monitor cervical cancer control services for women living with HIV: a policy brief

Published as:

Davidović M, Bohlius J: International Epidemiology Databases to Evaluate AIDS. Facility-based indicators to monitor cervical cancer control services for women living with HIV. R4d Policy Brief 2023, No. 1, December 2023. Available from: https://k4d.ch/facility-based-indicators-to-monitor-cervical-cancer-control-services-for-women-living-with-hiv/

Own contribution:

I participated in the conceptualization of the policy brief. I wrote the policy brief, prepared the visuals, and implemented comments from co-authors.

r4d programme

Policy Brief

no. 1 | 2023

Facility-based indicators to monitor cervical cancer control services for women living with HIV

In collaboration with the International epidemiology Databases to Evaluate AIDS (IeDEA) consortium, the Cervical Cancer Prevention and Care Cascade (CCPC Cascade) has been developed as a monitoring framework for routine patient-level data collection at HIV clinics offering cervical cancer prevention and care services in sub-Saharan Africa. The framework includes 17 facility-based indicators for performance measurement. Indicators can be adapted for use in different contexts.

Photo: A nurse conducting a visual inspection with acetic acid exam at a government health facility in Lusaka, Zambia. © Centre for Infectious Disease Research in Zambia

KEY MESSAGES

- The CCPC Cascade is a framework to measure the performance of steps along the cervical cancer prevention and care continuum for women living with HIV in sub-Saharan Africa.
- Five core and 12 optional CCPC Cascade indicators are recommended for routine patient-level data collection at ART clinics offering cervical cancer prevention and care services.
- A minimum set of data elements are required to inform the CCPC Cascade indicators.
- CCPC Cascade indicators should be selected based on local, programme, or facility priorities and data availability.

MAIN MESSAGE

Five core indicators and 12 optional indicators are recommended to inform the CCPC Cascade. Indicators were defined through a Delphi consensus process with 72 stakeholders working in 15 sub-Saharan African countries that are part of the IeDEA consortium.

How can we monitor and scale-up cervical cancer prevention and care services for women living with HIV in sub-Saharan Africa?
Cervical cancer is the leading cause of cancer mortality in women in sub-Saharan Africa. Women living with HIV are six times more likely to develop cervical cancer compared to women living without HIV. Of all women with cervical cancer and HIV globally, 85% live in sub-Saharan Africa, where 21% of all cervical cancer cases are attributable to HIV infection [1]. In 2020, the World Health Organization (WHO) launched the global strategy to eliminate cervical cancer as a public health problem. The aim of this strategy is to reduce the cervical cancer incidence rate to below four per 100,000 women per country within a century. The WHO proposed **90-70-90 targets by 2030** to accelerate these efforts: 90% coverage of HPV vaccination in girls, 70% coverage of cervical cancer screening, and 90% treatment and management of both precancerous lesions and invasive cancers [2, 3].

To reach the **90-70-90 targets,** the WHO recommended the introduction of HPV DNA testing as a primary screening test for women living with HIV, followed by a triage test (Figure 1). These services must be monitored and evaluated to allow policy makers to make evidence-based decisions and ensure the services are effective. To support monitoring efforts and improve the availability of high-quality data, the WHO published 'Improving data for decision-making: a toolkit for cervical cancer prevention and control programmes' [4] in 2018. This toolkit was developed by focusing on the secondary prevention portion of the continuum (screening and treatment of precancerous lesions). Although the toolkit suggested indicators and provided information to generate meaningful, actionable data for decision-making, it lacked specific indicators for high-risk populations like women living with HIV.

Advancing Cervical Cancer Screening in HIV-positive women (ACCHIVe) - The CCPC Cascade
To support existing cervical cancer control and monitoring efforts, the CCPC Cascade was tailored to girls and women living with HIV in sub-Saharan Africa. The **CCPC Cascade** is an innovative framework to monitor, and scale-up cervical screening services offered at antiretroviral treatment (ART) clinics. The CCPC Cascade is aligned to the current recommended cervical screening and treatment algorithms for women living with HIV [5] and follows the steps of the cervical cancer prevention and care continuum. For each step of the cascade, patient-level and facility-based indicators and data elements are recommended to inform these indicators, aiming to measure the performance of each specific step. The data collected and analyzed using the CCPC Cascade can be used to guide the decision-making process at the facility level.

First, a literature review was employed to extract relevant indicators, grouping them into domains along the cervical cancer control continuum at the facility level (Figure 2). From February 2021 to March 2022, **a three-round online Delphi consensus process** was conducted to reach agreement on indicators within IeDEA African region. **The Delphi consensus process** is an iterative, anonymous method to gather opinions and reach a consensus among a group of experts or stakeholders on a particular topic. This process followed recommendations from guidelines.

Stakeholders included experts in cervical cancer prevention and HIV/AIDS, healthcare professionals and clinicians, representatives of international health care organizations and government at the national, regional and district levels, public health experts, facility managers, and patient and community representatives. The Delphi process included **72 stakeholders from 15 countries in sub-Saharan Africa.** Through an anonymous, iterative process, they adapted the indicators to their local context (round 1), then rated based on five criteria – relevance, feasibility, comparability, reliability, and understandability – (rounds 2 and 3) and ranked them by importance (round 3). **Consensus** was reached if the indicator had a high level of agreement (more than 70% of respondents rated the indicator as high or very high on the Likert scale) in at least three of the five criteria listed above.

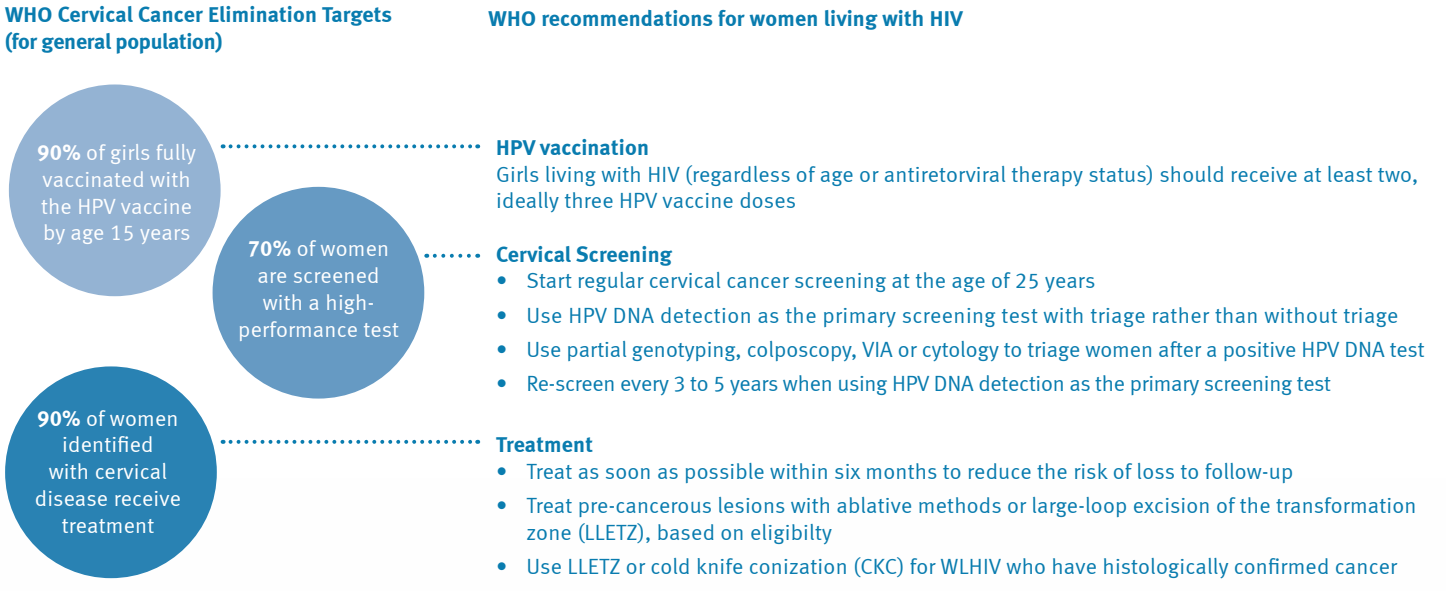

Figure 1 WHO cervical cancer elimination targets and recommendations for girls and women living with HIV.

Consensus was reached for **17 indicators** in the following domains: primary prevention (HPV prevention, n=2), secondary prevention (screening, triage, and treatment of precancerous lesions, n=11), tertiary prevention (cervical cancer diagnosis and care, n=2), and long-term programme impact and linkage to HIV services (n=2) (Figure 2). Five indicators had a high level of agreement in all five criteria **(core indicators):** 'Treatment rate of precancerous lesions', 'cervical screening rate', 'number of women screened for cervical pre-cancer', 'screening test positivity rate', and 'screening test positivity rate for first-time screened women'. The other 12 indicators **(optional indicators)** had a high level of agreement in three or four criteria.

Conclusions, implications, and recommendations

Stakeholders from 15 countries reached consensus on **five core and 12 optional indicators** to evaluate performance along **the CCPC Cascade**, a framework for routine patient-level data collection at ART clinics that offer cervical cancer prevention and care services in sub-Saharan Africa. Minimum data elements (Table 1) to be collected and reported to inform

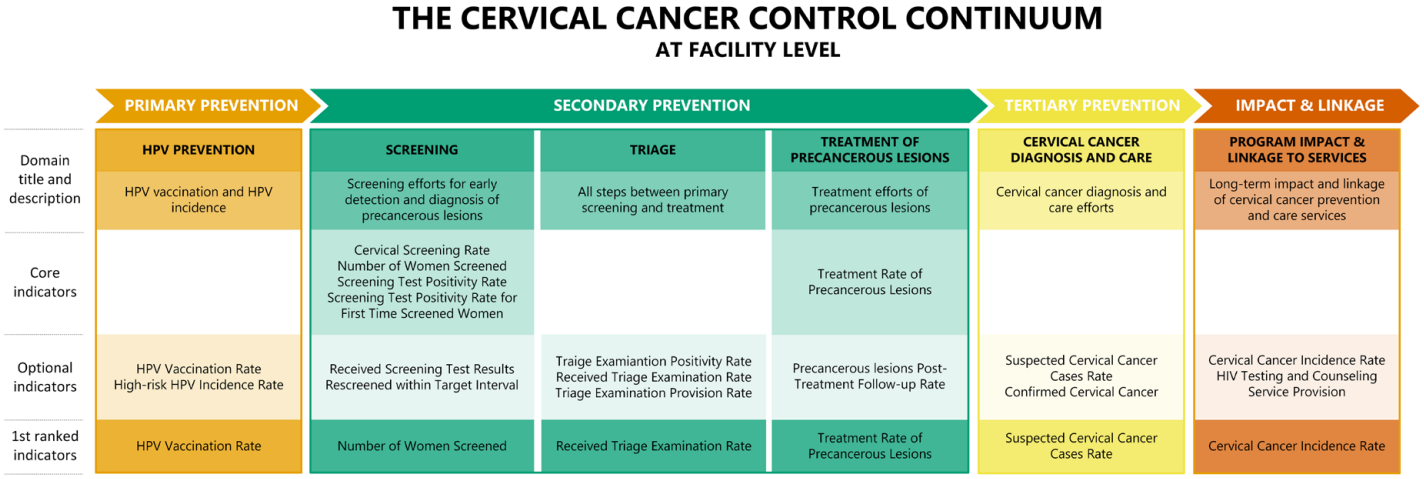

Figure 2 The Cervical Cancer Control Continuum at facility level: the overview of domains, core, optional and 1st ranked indicators per each domain that reached consensus in Round 3. Source: Davidović M et al, on behalf of the IeDEA (In press). Facility-based indicators to manage and scale up cervical cancer prevention and care services for women living with HIV in sub-Saharan Africa: three-round online Delphi consensus method. JAIDS.

The minimum data set required:	Enrollment into HIV care[1]	Screening visit	Screening / triage Results[2]	Treatment for pre-cancer	Age	Screening visit type[3]	Screening / triage methods[4]	Treatment methods[5]	Received HIV testing and counseling service	HPV vaccination	Biopsy results
Core indicators											
Number of women screened for cervical pre-cancer		X			D	D	D				
Cervical Screening Rate	X	X			D	D	D				
Screening test positivity rate for the primary screening test		X	X		D	D	D				
Screening test positivity rate for the primary screening test for first time screened women		X	X		D	X	D				
Treatment rate of precancerous lesions			X	X	D	D	D	X			
Optional indicators											
Suspected Cervical Cancer Cases Rate		X	X		D	D	D				
Triage Examination Positivity Rate		X	X		D	D	D				
Cervical Cancer Incidence Rate	X				D						X
High Risk HPV Incidence Rate		X	X		D						
Confirmed Cervical Cancers		X	X		D	D	D				
HPV Vaccination Rate	X				D					X	
Precancerous Lesions Post-Treatment Follow-Up Rate				X	D	X		D			
Received Screening Test Results		X	X		D	D	D				
Rescreened within Recommended Screening Interval		X			D	X	D				
HIV Testing and Counseling Service Provision Rate		X			D				X		
Received Triage Examination Rate		X	X		D	D	D				
Triage Examination Provision Rate		X	X		D	D	D				

Abbreviations: X – Data element required; D – Data element needed for additional disaggregation.

Table 1 Indicators are ordered by the rating results from the third round.
[1] Key population: women living with HIV/AIDS 25-49 years old enrolled in care with at least one ART clinic visit during the period of interest.
[2] Screening / Triage results: according to WHO guidelines.
[3] Screening visit: First-time Screening; Post-treatment Follow-up Screening; Rescreening.
[4] Screening / triage results: HPV test; VIA/VILI; Pap smear / cytology; and colposcopy.
[5] Treatment methods for precancerous lesions: cryotherapy and LEEP.

the CCPC Cascade indicators are proposed. These indicators should support programme and data managers, stakeholders, and health professionals to better understand the performance of each step along the cervical cancer prevention and care continuum for girls and women living with HIV, leading them towards evidence-based decision-making.

These indicators were tailored to ART clinics that offer on- and/or off-site cervical cancer prevention and care services. In collaboration with the IeDEA consortium, the data needed to inform the CCPC Cascade indicators will be implemented within the IeDEA Data Exchange Standard. This will help to manage cervical cancer control services in ART clinics in sub-Saharan Africa. The CCPC Cascade indicators can be implemented gradually and adapted to context in other countries. This will facilitate standardized data collection and reporting, and inform decision-making processes to improve or scale-up cervical cancer screening and care services. Ultimately, the aim is to strengthen capacities for analyzing, interpreting, and sharing cervical cancer data, and to support existing efforts [6] to reach the goals of the WHO Cervical Cancer Elimination Strategy [2].

ABOUT THE ACCHIVE PROJECT

The Advancing Cervical Cancer Screening in HIV-positive women (ACCHIVe) project involves a team of cancer researchers and health professionals from Zambia (Cervical Cancer Prevention Programme, University Teaching Hospital, and Centre for Infectious Disease Research) and Switzerland (Swiss Tropical and Public Health Institute, University of Basel). The ACCHIVe project is being undertaken in collaboration with the IeDEA International epidemiology Databases to Evaluate AIDS consortium, a network that curates and analyzes data from routine HIV treatment and care sites in 22 countries across four African regions (Central, East, Southern, and West Africa).

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FURTHER INFORMATION ABOUT THE PROJECT AND RELATED PUBLICATIONS

Advancing Cervical Cancer Screening in HIV-positive women (ACCHIVe) – The Cervical Cancer Prevention and Care Cascade: here

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ABBREVIATIONS:

AIDS – Acquired Immune Deficiency Syndrome
ART – antiretroviral treatment
DNA – Deoxyribonucleic acid
HIV – Human Immunodeficiency Virus
HPV – Human Papillomavirus
VIA – Visual Inspection with Acetic Acid
WHO – World Health Organization

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Indicators and targets for cervical cancer prevention in countries with the highest HIV burden: A scoping review protocol

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Abstract

Introduction

Inequities and inequalities in cervical cancer (CC) incidence and mortality persist between high- and low-income countries. In several countries with high human Immunodeficiency virus (HIV) prevalence, prevention strategies and particularly screening, have been integrated in antiretroviral treatment (ART) programmes. However, these programmes are undermined by a lack of functional monitoring systems for women screened for precancerous cervical lesions or diagnosed with invasive CC.

Health policies provide a blueprint for programme implementation, tailored to the health needs of the population. For these programmes to be effective, monitoring and evaluation frameworks with clearly defined indicators and targets that track programme performance and ultimately outcomes of women screened are needed.

Objective

This scoping review will identify and assess consistency of indicators and targets for CC prevention and control programmes in countries with the highest HIV prevalence. We will use the WHO toolkit for CC prevention and control programmes and the WHO draft global strategy to eliminate CC as a public health problem as reference documents to check policy alignment with global indicators and targets.

Methods

We will use the enhanced version of Arksey and O'Malley's methodological to conduct this review. Reporting will be guided by the Preferred Reporting Items for Systematic Reviews and Meta Analyses extension for scoping reviews (PRISMA-ScR).

We will conduct a search for policies, strategies, plans for cervical cancer, cancer and non-communicable diseases control on https://www.iccp-portal.org/map. We will also conduct a search for documents not registered on this website on MEDLINE (via Ovid and Pubmed), Google Scholar, and national data repositories of participating countries (when available). We will also consult experts in participating countries for other relevant information.

Results and dissemination

We will present results of this review at conferences and submit for publication in a peer-reviewed journal. The current study will contribute towards the development of a CC prevention and care cascade in SSA.

Introduction

Cervical cancer (CC) incidence and mortality rates are projected to rise in the next decade[1]. The greatest burden is borne by Sub-saharan Africa, exacerbated by the high Human Immunodeficiency Virus (HIV) prevalence in this region. Women living with HIV (WLHIV) are more prone to persistent human papillomavirus (HPV) infection, precancerous lesion development and rapid progression to invasive CC[2].

In high-income countries, effective screening programmes have reduced CC incidence by about 80% in over three decades.[3,4] However, many low and middle-income countries, have yet to witness this reduction, due to competing health priorities, resource challenges and a general lack of monitoring and evaluation systems for existing programmes. Several countries, South of the Sahara have integrated cervical screening into existing antiretroviral therapy (ART) services, a strategy which has been shown to be feasible and acceptable and an effective way to improve access to cervical screening[5]. Such a model maximizes the many contacts women have with the health system (antenatal clinics, Family Planning units, vaccination units, ART clinics), thus improving coverage and potentially, follow-up of screened women.

In order to assess effectiveness of these programmes, there is need for a monitoring and evaluation system with indicators that measure progress towards achieving the set

goals. Such monitoring frameworks are crucial in identifying gaps and taking timely corrective measures to optimize gains for efforts. World Health Organisation (WHO) recommends 'a functioning monitoring system to track HPV vaccination, screening and follow-up treatment' as an essential requirement for a comprehensive CC prevention and control program[6]. Developing indicators and tools to monitor and assess programme performance is an essential part of the planning phase for the implementation of quality control for a CC control program[7]. Assessing the impact of prevention efforts furnished by countries requires a comprehensive monitoring and evaluation framework, which includes indicators that monitor service delivery and progress towards defined targets.

Objective

The purpose of this scoping review is to identify indicators and targets for CC prevention and control programmes in countries with the highest HIV burden while assessing consistency with recommended global indicators and targets.

Methods and design

We will use the revised Arksey and O'Malley scoping review methodological framework[8] for the current study. It is a six-item framework, which guides scoping review conduct. It provides recommendations and further clarification for all items. The Preferred Reporting Items for Systematic Reviews and Meta Analyses extension for scoping reviews (PRISMA-ScR)[9] will guide reporting of this review.

PRISMA-ScR is a 22-item checklist for reporting scoping reviews adapted from the PRISMA checklist. This tool excludes 5 items (13, 15, 16, 22, 23) from the 27- item PRISMA checklist not relevant for scoping reviews. Two of the 22 items are optional: critical appraisal of individual sources of evidence and critical appraisal within sources of evidence.

Inclusion Criteria

1. We will include the most recent versions of policy documents that contain aspects of CC prevention and control in countries with HIV prevalence greater than or equal to 10%. This arbitrary cut-off corresponds to nine countries in Southern Africa: Swaziland, Lesotho, Botswana, South Africa, Namibia, Zimbabwe, Zambia, Mozambique and Malawi. Standalone CC prevention and control documents will take precedence over general plans for cancer control or non-communicable diseases control. There will be no language restrictions.

Exclusion criteria

We will exclude general cancer control plans where a recent standalone CC prevention and control document is available.

Methodological framework

Identifying the research question

The WHO toolkit for CC prevention and control programmes, and the draft global strategy to eliminate CC as a public health problem provides the basis for our inquiry. The toolkit defines a wide range of indicators disaggregated by different variables including HIV status and recommends key indicators to be included in monitoring and evaluation systems for global monitoring of cervical cancer prevention and control programmes. The global strategy defines global targets to be met by programmes in order to achieve CC elimination within a century. As described by Levac et al[3], we will link the purpose of our study with our research questions. (include the scope of inquiry, the definition of the concept, target population and outcomes of interest in the definition of our research questions).

Questions- Objectives

1. What performance and result indicators are recommended for CC prevention in countries with the highest HIV prevalence?
    1. How are these indicators defined? (numerators and denominators?)
    2. How do these indicators and their definitions align with the core indicators recommended by WHO for programme monitoring?
2. What targets are defined for HPV vaccination, cervical screening and treatment of precancerous lesions and invasive cancer?
3. What are the tools available for programme monitoring and evaluation?

Identifying relevant documents and policies

We will use the portal of the International Cancer Control Partnership that provides resources for cancer control planners. It contains a comprehensive but non-exhaustive list of cancer control plans). Two researchers will identify policy documents relevant to CC prevention and control through website searches on https://www.iccp-portal.org/map (which contains a comprehensive but non-exhaustive list of cancer control plans). Country experts will also be consulted for unpublished documents.

We will also conduct a search to identify other policy documents for CC prevention and control for these specific countries on MEDLINE (via Ovid and Pubmed), Google Scholar, and national data repositories (when available). Our search terms will constitute a combination of Medical Subject Headings (MeSH) terms and key words including but not limited to: Human papillomavirus vaccination AND Cervical cancer screening AND Cervix screening AND screening for precancerous lesions AND Cervical cancer prevention AND Cervical cancer control AND cancer control AND cancer prevention and control AND non-communicable diseases control policy OR plan OR strategy OR guideline AND Botswana OR Namibia OR Malawi OR South Africa OR Mozambique OR South Africa OR Zambia OR Zimbabwe.

Our search strategy will also be guided by the suggested list of documents for a desk review in the toolkit for CC prevention and control, such as: strategic health plan, cancer screening policy or strategic plan, national cancer prevention and control policy, HPV vaccination policy or strategic plan, national cervical cancer treatment policy or strategic plan, policy relevant to any aspect of cervical cancer screening, national clinical practice guidelines for cervical cancer screening, clinical practice guidelines for cervical cancer screening specific to HIV infected women, national clinical practice guidelines for the management of invasive cervical cancer, policies and clinical practice guidelines used for cervical cancer screening and treatment of invasive cancer.

Document selection

Two reviewers will independently conduct the guideline search and save them in a Mendeley library. They will screen for eligibility of policy documents focusing on titles, executive summaries and overviews. They will further assess the full texts of the documents and retain eligible ones where inclusion information is not captured in the title, executive summary nor overview. The team has met to discuss study inclusion criteria.

Charting the data

A standardized data extraction sheet will be used to extract data from included documents. Data items to be collected will include country, title of the plan, period of validity, information on human papillomavirus vaccination, cervical screening methods and strategies, treatment methods, indicators and targets for monitoring HPV vaccination, screening and treatment.

Two researchers will independently extract data and both extractions will be compared. A third researcher will resolve discrepancies that may arise in the review process. All identified indicators will be summarized in the final narrative, separating HIV-specific indicators.

Collating, summarizing and reporting results

We will report results using descriptive numerical summaries and themes that provide clarity on indicators for monitoring and targets. Indicators will be reported according to stage of the continuum: HPV vaccination, screening, treatment and care. Indicators specific to the HIV population will be reported separately under the same categories. We will classify identified indicators to reflect different stages in the continuum of care.

Consultation (optional)

We have already consulted some CC prevention and control experts in some participating countries for relevant policy documents.

Potential amendments

Any amendments to the present protocol during the review process will be reported.

Conclusion

This review will summarise indicators and targets for CC prevention and control programmes in sub Saharan African countries with the highest HIV prevalence. We will report indicators under CC prevention and care, highlighting indicators specific to the HIV population. We will also extract definitions of recommended indicators in policy documents and assess consistency across countries and with WHO recommended global indicators and targets. This review will also inform the development of a CC prevention and care cascade in SSA and will form one chapter of a PhD thesis.

Ethics and dissemination

No ethics approval is recommended for this study. This narrative review will inform a cervical cancer prevention and care cascade for low- and middle-income countries under development.

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Disclaimer

Portions of this thesis were proofread with the assistance of AI-based technology, including ChatGPT provided by OpenAI. The utilization of such technology was aimed at enhancing the grammatical accuracy and readability of the text. The final content, analysis, visualizations, and conclusions presented in this PhD thesis were exclusively written and developed by me. The thematic elements featured at chapter pages were conceptualized by me and designed by Susana Pérez.

11. SUPPLEMENTARY INFORMATION OF INDIVIDUAL PUBLICATIONS

11.1. Supplementary Information Publication 1

Davidović M, Asangbeh SL, Taghavi K, et al; International Epidemiology Databases to Evaluate AIDS. Facility-Based Indicators to Manage and Scale Up Cervical Cancer Prevention and Care Services for Women Living With HIV in sub-Saharan Africa: a Three-Round Online Delphi Consensus Method. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2024 Feb 1;95(2):170-178.

The supplementary information is available from: https://doi.org/10.1097/QAI.0000000000003343, accessed on March 13, 2024.

Table of content

Supplementary Tables and Figures

Table S1. Survey rates calculations

Rate	Definition
Response rate	Number of participants who completed the survey / number of emailed participants
Completion rate	Number of participants who completed the survey / number of participants who agreed to participate in the survey
Participation rate	Number of participants who started the survey / number of emailed participants

Note: the same equations were used for each round.

Table S2. List of documents reviewed and number of extracted indicators

Country*	Year†	Title	Language	Resource	No. ‡
Central Africa					
Burundi	2019-2023	Plan d'action Multisectoriel de Prevention et de Controle des Maladies non Transmissibles	French	ICCP	1
Cameroon	2020-2024	National Strategic Plan for Prevention and Cancer Control	English	ICCP	14
Rwanda	2020-2024	Rwanda National Cancer Control Plan	English	ICCP	26
East Africa					
Kenya	2019-2030	Kenya Cancer Policy	English	ICCP	3
	2017-2022	National Cancer Control Strategy	English	ICCP	23
	2012-2015	National Cervical Cancer Prevention Program Strategic Plan	English	ICCP	18
Tanzania	2016-2020	Strategies and Action Plan for the Prevention and Control for NCDs in Tanzania	English	ICCP	5
	2013-2022	National Cancer Control Strategy (NCCS)	English	ICCP	34
Uganda	2010-2014	Strategic Plan for Cervical Cancer Prevention and Control in Uganda	English	ICCP	23
Southern Africa					
Botswana	2018-2023	Botswana National Multisectoral Strategy for the Prevention and Control of Non- Communicable Diseases	English	ICCP	7
	2017-2022	Botswana National Multisectoral Strategy for the Prevention and Control of Non-Communicable Diseases	English	ICCP	15
	2010-2020	Integrated health service plan: Strategy for Changing the Health Sector For Healthy Botswana	English	Expert	3
Eswatini	2019-2022	National Cancer Control Plan	English	ICCP	6
	2018	National Prevention and Control of NCDs - annual programme report	English	Expert	2
Lesotho	2017-2022	Lesotho National Health Strategic Plan (NHSP)	English	Expert	4
	2014-2020	Lesotho National multi-sectoral integrated strategic plan for prevention and control of NCDs	English	ICCP	1
	2012	Guidelines for screening for cervical precancer in Lesotho	English	Expert	14
Malawi	2019-2029	National cancer control strategic plan	English	ICCP	0
	2019	Standard Operating Procedures for Cervical Cancer Services	English	Expert	12
	2016-2020	National Cervical Cancer Control Strategy	English	ICCP	5
Mozambique	2019-2029	National Plan for Cancer Control	English	ICCP	0
Namibia	2017-2022	National Strategic Framework for HIV and AIDS Response in Namibia	English	Expert	1
	2017-2022	National Multisectoral Strategic Plan for Prevention and Control of Non-Communicable Diseases (NCDs) in Namibia	English	ICCP	6
South Africa	2017-2020	National Cancer Strategic Framework	English	ICCP	12
	2017	Cervical Cancer Prevention and Control Policy	English	ICCP	9
	2013-2017	Strategic Plan for the Prevention and Control of NCDs	English	ICCP	2
Zambia	2016-2021	National cancer control strategic plan	English	ICCP	11

	2015	Visual Inspection with Acetic Acid and Cryotherapy - A Reference Manual for Trainers and health Care Providers	English	Expert	27
	2013-2016	Non-Communicable Diseases and Their Risk Factors, Zambian Strategic Plan	English	ICCP	1
Zimbabwe	2016-2020	The Zimbabwe cervical cancer prevention and control strategy	English	Expert	11
	2014-2018	National cancer prevention and control strategy for Zimbabwe	English	ICCP	17
West Africa					
Burkina Faso	2013-2017	Plan Stratégique de lutte contre le cancer	French	ICCP	2
Cote d Ivoire	2015-2019	Politique Nationale de Prévention et de Prise en charge des Maladies Chroniques Non Transmissibles en Côte d'Ivoire	French	ICCP	7
Ghana	2012-2016	National Strategy for Cancer Control in Ghana	English	ICCP	32
	2012-2016	Strategy for the Management, Prevention and Control of Chronic Non-Communicable Diseases	English	ICCP	4
Mali	2019-2023	Plan Strategique Integre de Lutte Contre les Maladies Non Transmissibles (MNT)	French	ICCP	4
Senegal	2015-2019	Plan strategique de lutte contre le cancer	French	ICCP	12
Togo	2018-2022	Politique National et Plan Stratégique Intégré de lutte contre les MNT	French	ICCP	4
	2017-2022	Le Plan stratégique pour la prévention et le contrôle du cancer du col de l'utérus	French	ICCP	12
International					
PAHO	2016	Integrating HPV testing in cervical cancer screening program: a manual for program managers	English	WHO	4
PEPFAR	2019	Monitoring, Evaluation, and Reporting Indicator Reference Guide	English	PEPFAR	2
UNAIDS	2021	Global AIDS Monitoring 2022	English	UNAIDS	3
WHO	2020	WHO Framework for strengthening and scaling-up services for the management of invasive cervical cancer	English	WHO	5
	2018	Improving data for decision-making: a toolkit for cervical cancer prevention and control programmes	English	WHO	52
	2014	Comprehensive Cervical Cancer Control - A guide to essential practice Second edition	English	WHO	15
WHO & PAHO	2013	Monitoring national cervical cancer prevention and control programmes: quality control and quality assurance for visual inspection with acetic acid (VIA)-based programmes	English	WHO	8
Websites					
WHO / IARC	2019	Cancer Screening in Five Continents (CanScreen5) https://canscreen5.iarc.fr/CervixQEN.pdf	English	Web Tool	27
NordScreen	2019	NordScreen: Performance indicators on cancer screening in the Nordic countries	English	Web Tool	3
				Total:	**509**

*Sorted in alphabetic order for each region; † year of publication or of the plan period; ‡ Numbers of indicators extracted; Abbreviations: ICCP – The International Cancer Control Partnership, https://www.iccp-portal.org/; WHO – World Health Organization, https://www.who.int/initiatives/sdg3-global-action-plan/resources ; PAHO – Pan American Health Organization; PEPFAR – The United States President's Emergency Plan for AIDS Relief; UNAIDS – Joint United Nations Programme on HIV/AIDS; IARC – International Agency for Research on Cancer

Table S3. Self-reported characteristics of the Expert Panel members

General characteristics of participants		R1	R2	R3	Total*
General	Invited	85	84	101	106
	Participated	46	40	55	72
	Participated in previous round(s)*	n.a	35	49	38§
	Finished	29	34	45	54
Response rate	# of participants who completed the survey / # of emailed participants	34%	40%	45%	n.a
Completion Rate	# of participants who completed the survey / # of participants who agreed to participate in the survey	63%	85%	82%	n.a
Participation rate	# of participants who started the survey / # of emailed participants	54%	48%	54%	n.a
Preferable Language	English	21	25	35	44
	French	8	9	10	10
Gender	Female	15	19	22	28
	Male	14	15	23	26
IeDEA Collaborator	Yes	20	27	34	38
	No	7	6	8	12
	Uncertain	2	1	3	4
IeDEA Region	Central Africa	2	3	4	4
	East Africa	6	5	5	9
	West Africa	7	6	9	9
	Southern Africa	11	16	22	26
	Globally/internationally	3	4	5	6
IeDEA Central Africa	Cameroon	0	0	1	1
	Rwanda	0	1	1	1
	Republic of the Congo	1	1	1	1
	Democratic Republic of the Congo	1	1	1	1
IeDEA East Africa	Kenya	3	3	4	4
	Tanzania	3	2	0	4
	Uganda	0	0	1	1
IeDEA West Africa	Côte d'Ivoire	7	6	8	8
	Nigeria	0	0	1	1
IeDEA Southern Africa	Lesotho	1	1	1	1
	Malawi	0	0	1	1
	Mozambique	0	1	2	2
	South Africa	4	5	5	6
	Zambia	1	3	6	7

	Zimbabwe	3	3	3	5
	Other	2‖	3‖	4‖	4
Main role at the current work	Researcher with focus on cervical cancer prevention or HIV/AIDS	15	17	22	24
	Health care professional / clinician	10	10	10	14
	Representative of international health care organization	2	3	3	4
	Public health expert	2	3	2	4
	Representative of health ministry or government at national, regional or district level	0	1	1	1
	Health facility manager	0	0	1	1
	Information system officer	0	0	1	1
	Patient/community representative	0	0	1	1
	Other	0	0	4	4
Expertise†	Cervical cancer prevention and care	14	17	24	29
	HIV/AIDS care and treatment	8	9	12	14
	Other	7	6	9	10
Experience Level in cervical cancer prevention and care	No experience	0	0	1	1
	Less than 5 years	9	11	14	16
	5-10 years	4	6	11	14
	10-20 years	15	16	16	20
	20+ years	1	1	3	3
Experience Level in HIV/AIDS care and treatment	No experience	5	6	8	9
	Less than 5 years	2	4	4	6
	5-10 years	2	4	5	6
	10-20 years	8	9	11	14
	20+ years	4	4	5	5
	No answer	8	7	12	14
Experience Level – Other (optional)‡	Less than 5 years	3	3	2	3
	5-10 years	2	2	3	3
	10-20 years	4	4	6	8
	20+ years	1	1	1	1

*Total number of responses of unique participants who participated in at least one round, therefore the numbers from previous rounds do not sum up; † No answer or more than one answer were possible; ‡ for the list of other experience, look Supplementary Table 6; n.a – non-applicable; § 38 out of 54 (70%) participants in Round 3; ‖Working in more than one country; ¶ Biostatistician; Program Officer; Researcher with other primary focus; and Monitoring and Evaluation Officer at the National Cancer Control Program; Abbreviations: # - number, IeDEA – International epidemiology Databases to Evaluate AIDS.

Table S4. Other experiences reported by the Expert Panel members

Other listed experiences*	
Research oriented	Cancer Epidemiology/Research
	Clinical Research
	HIV Epidemiology/Research
	Infections Disease Epidemiology/Research
	Non Communicable Diseases Epidemiology/Research
	Perinatal Research
	Public Health Research
Health Care System oriented	Data Management/Harmonization
	Evaluation of the Screening Programs
	Monitoring and Evaluation
	National Cervical Cancer Governance
Clinically oriented	Family Planning
	Kaposi Sarcoma
	Obstetrics And Gynecology
	Tuberculosis Care And Treatment
Other	Education
	Implementation Science
	HIV Prevention; Gender-Based Violence Prevention and Response
	Systematic Literature Reviews

*reported by the Expert Panel members in rounds 2 and 3, summarized and grouped by similarity

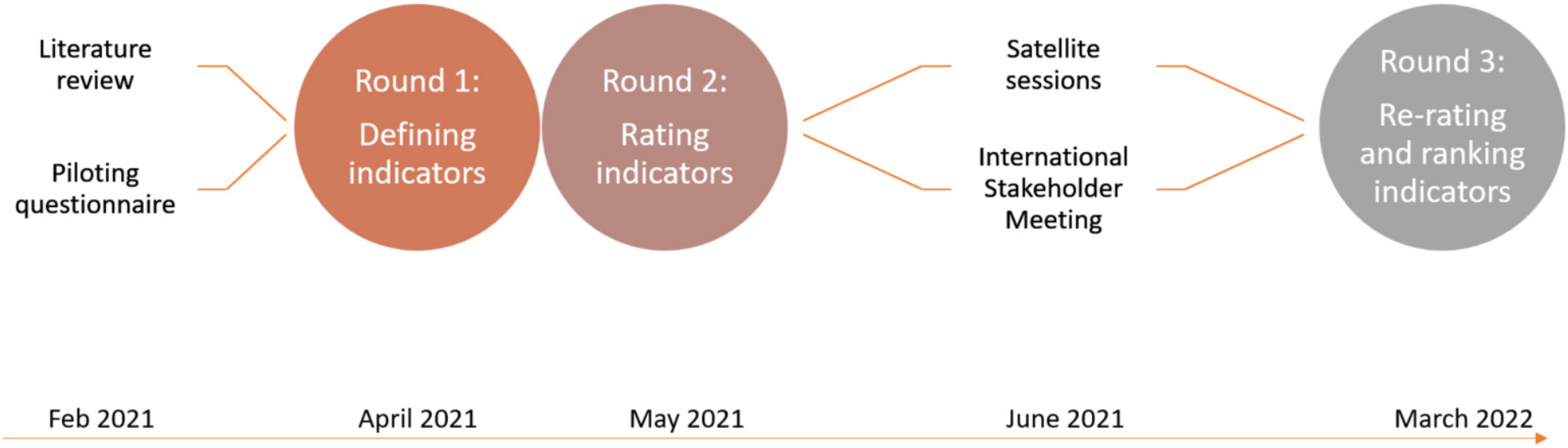

Figure S1. Three-round online Delphi process

Domain †	Indicator Name	Rating Criteria: Relevance R2	Relevance R3	Feasibility R2	Feasibility R3	Comparability R2	Comparability R3	Reliability R2	Reliability R3	Understandability R2	Understandability R3	# of Criteria‡ R2	# of Criteria‡ R3
6	Cervical Cancer Mortality Rate	91%	93%	56%	47%	71%	60%	56%	42%	94%	96%	3	2
6	Cervical Cancer Survival Rate	85%	89%	44%	51%	71%	58%	50%	53%	82%	89%	3	2
4	Precancerous Lesions Cure Rate	94%	93%	53%	58%	74%	64%	59%	58%	94%	91%	3	2
5	Suspected or Confirmed Cervical Cancer Treatment and Follow-Up Rate	82%	93%	41%	58%	76%	64%	56%	51%	88%	87%	3	2
4	Precancerous Post-treatment Complication Rate	74%	78%	53%	51%	62%	53%	47%	53%	79%	96%	2	2
5	Suspected Cervical Cancer Referral Rate	79%	78%	50%	58%	65%	67%	50%	56%	79%	91%	2	2
3	Triage Referral Compliance Rate	71%	76%	38%	47%	56%	60%	41%	51%	71%	76%	2	2
5	Suspected Cervical Cancer Referral Compliance Rate	68%	78%	35%	38%	56%	60%	38%	33%	71%	82%	1	2
6	Linkage to HIV Services	62%	78%	53%	69%	59%	58%	56%	67%	65%	84%	0	2
3	Received Triage Results	68%	84%	41%	58%	56%	67%	47%	64%	65%	87%	0	2
2	Inadequate Sample Rate	59%	67%	56%	47%	56%	60%	53%	44%	68%	76%	0	1
3	Referred for Triage Rate	65%	69%	35%	42%	62%	51%	44%	47%	65%	78%	0	1
2	Screening Test Failure Rate	41%	60%	35%	44%	44%	47%	41%	36%	59%	71%	0	1
	Total # of indicators that reached 70% agreement	7	10	0	0	4	0	0	0	8	13		

† Domains: 1) Primary prevention – HPV prevention; 2) Secondary prevention – Screening; 3) Triage; 4) Treatment of precancerous lesions; 5) Tertiary Prevention – CC diagnosis and care; 6) Program impact and linkage to HIV services; # Number; ‡ Number of criteria – the number of criteria with high level of agreement (> 70 % participants rated as 4 (High) or 5 (Very high) points on the Likert scale). Indicators are ordered by highest to lowest number in R3, followed by the highest to lowest number in R2; Abbreviations: R2 – Round 2; R3 – Round 3. Note: Consensus was reached if more than 70% of participants rated the indicator as 4 (High) or 5 (Very high) points on the Likert scale in 3 or more criteria

Figure S2. List of indicators that did not reach consensus in Round 3

File S1: Inclusion criteria for the Expert Panel members

Inclusion criteria for selecting the Expert Panel members

- Representing one of 4 IeDEA African Region or experts whose work is focused in cervical cancer prevention or HIV/AIDS prevention and care in sub-Saharan Africa
- ≥1 year of experience
- Available to participate for the whole period of the study
- Declare no conflict of interest
- Willingness to participate
- Sufficient language knowledge (English or French)
- Recommended by members of Working Group or IeDEA Collaborators
- Country of residence and work in sub-Saharan region

Types of experts and stakeholders

- Researchers with focus on cervical cancer prevention or HIV/AIDS
- Health care professionals
- Representatives of Ministry of governance at national, regional or district level
- Representatives of local and national NGOs
- Patient/community representatives
- Public health experts
- Representatives of international health care organizations
- Information system officers
- Health facility managers
- Representatives of funders

If you have any other questions, please do not hesitate to reach us via survey.cascade@gmail.com

File S2: Delphi methodology

Three-round online Delphi process

In our study we conducted a three-round online Delphi process (Figure S1), following recommendations from guidelines and reviews [1-6]. To reach agreement on different aspects of the Delphi process, we conducted an internal online survey using the Qualtrics^{XM} Software among three of our core team members (JB, PVG and KT). We discussed and resolved any disagreements in the results by consensus. Members answered questions related to:

- The selection criteria for the Expert Panel Members
- Types of professions of the Expert Panel members
- Number of rating criteria to be used in the Delphi process
- Selection of rating criteria
- Number of the Likert scale points to be used in the rating process
- Definition of consensus

The survey items were based on a literature review we conducted and the available guidelines for the Delphi methodology [1-4, 7]. We piloted the questionnaire among team members, IeDEA regional principal investigators, and experts recommended by the principal investigators.

Selection criteria for the Expert Panel members

The selection criteria chosen by all three team members are defined as “high importance", the criteria that two team members voted for are defined as “middle importance”, and the criteria only one team member voted for are defined as “low importance”. One criterion (age of participants) was excluded because it received no vote. We applied the level of importance in the selection of Expert Panel members, giving priority to members that fulfilled “high importance” criteria (Table S1).

File S2 Table S1. *Selection criteria for the Expert Panel members*

High importance	Representing one of 4 IeDEA African Regions (Southern, Central, East, West)
	Experts whose work is focused on cervical cancer prevention or HIV/AIDS prevention and care in sub-Saharan Africa
	Years of experience
Middle Importance	Available to participate for the whole period of the study
	Declare no conflict of interest
	Willingness to participate
Low importance	Language knowledge (English, French)
	Recommended by members of Working Group or IeDEA Collaborators
	Country of residence and work

The Expert Panel composition

Team members rated different expert and stakeholder professions to be invited to the Expert Panel. Professions that all team members voted for are defined as “high importance", professions that two team members voted for are defined as “middle importance”, and professions that one team member voted for are defined as “low importance”. We applied the level of importance in the selection process, giving a priority to specific “high importance” professions (Table S2).

File S2 Table S2. *Professions of experts and stakeholders*

High importance	Researchers with focus on cervical cancer prevention or HIV/AIDS
	Health care professionals
	Representatives of health ministry or government at national, regional or district level
	Representatives of local and national non-governmental organizations
	Patient/community representatives
Middle Importance	Public health experts
	Representatives of international health care organizations
	Information system officers
Low importance	Health facility managers
	Representatives of funders

Definition of consensus

We extracted the most commonly used definitions of consensus from the literature [5, 6]. Team members voted for the following definitions and examples:

a) Percent agreement

For example, if at least 80% participants rated in the certain rate (to be defined additionally), the consensus is reached.

b) Median score greater than a predefined threshold

For example, when using nine-point Likert scale, the consensus is reached if the median score is greater or equal to 7.

c) The proportion of rating within a range: median score above the predefined threshold and a high level of agreement among panel members.

For example, if 75% or more of the experts gave the median scoring 7+ on a nine-point Likert scale, the consensus is reached.

d) Other, please specify:_____

Team members agreed to use the proportion of rating within a range: median score above the predefined threshold and a high level of agreement among panel members. We defined in person the threshold and a high level of agreement as: more than 70% of respondents rated an indicator as 4 (high) or 5 (very high) points on the Likert scale on at least three of the five criteria.

Rating Criteria

The team members rated the list of criteria extracted from the literature based on importance or suggested other criteria. There was no limit on the number of potential criteria. The team members agreed to use five criteria, those that had two and three votes. The criteria that had zero votes or one vote were excluded. The selected criteria and their definitions are presented in Table S3.

File S2 Table S3. *Rating Criteria*

Criteria	Definition
Relevance	The quality or state of being closely connected or appropriate
Feasibility	Possible to carry out the proposal data collection under normal program conditions; the state or degree of being easily or conveniently done
Comparability	Generates corresponding or parallel values across different population groups or geographical cites
Reliability	The quality of being trustworthy or of performing consistently well; it produces the same results when used more than once to measure the same condition or event; it is accurate and consistent through repeated measurement
Understandability	Capable of being understood

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File S3: Meeting minutes

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We would like to thank you for your support and inputs.

We truly appreciate your participation!

The Cascade Team

For any additional information, please contanct us: survey.cascade@gmail.com

Last time updated: July 2023

Summary of discussion points in satellite sessions

Discussion points: age range of the key population

- *What are your concerns regarding the selection of age range?*
- *What solutions or ideas are emerging now?*

Discussion points: the key population

- *What are your concerns regarding the selection of the key population?*
- *What solutions or ideas are emerging now?*

Discussion points: Target population for HPV vaccination indicator

- *Is this applicable to define target population for girls for HPV vaccination?*
- *Proposals for target population definition (HPV vaccination indicator)*

Discussion points: age range for HPV vaccination indicator

- *What are your concerns regarding the selection of age range?*
- *Proposals for age range*

Discussion points: treatment of cervical precancer

- *At HIV facility level, is it feasible to document and report this data? What are your concerns/challenges?*
- *What solutions or ideas are emerging now?*

Discussion points: treatment of cervical cancer

- *How could this indicator be simplified?*
- *How could a simplified indicator be formulated?*

Discussion points: triage indicators

- *What concerns and challenges do you see regarding the documentation and reporting of the core triage indicators at HIV facility level?*
- *What can you do to advance the monitoring of triage? What do you need for this?*

Discussion points: targets and benchmarks

- *What arguments do you see for using targets and benchmarks for IeDEA Cascade indicators?*
- *What arguments do you see against using them?*

Meeting minutes

Satellite Session 1

Date: Monday, 14th of June, 2021

Time: 15:00 – 17:00 CEST time

Aim of the session

Discuss and agree on definitions for:

- Age range for screening in women living with HIV
- Key population

Discussion points: age range

What are your concerns regarding the selection of age range?

Concerns regarding the age range:

- Women do not know their age
- Affordability of HPV screening
- Recommendations vs Reality of care delivery
- Registers do not have disaggregated data
- Feasibility of HPV test screening in some settings
- Screening not addressed to women older than 60
- Also the concern of confusion for patients and communities if there are conflicting guidance on age range
- Different national guidelines depending on whether it concerns HIV+ women or general women population
- Weak evidence underpinning age range decisions
- Young end – push to start earlier, but some HPV infection is transient, could lead to over treatment
- Older age – should be flexible as 2-life time screens should be available, even if later that 40 years
- Concern of age linked to test type, noting that via is only relevant for premenopausal women
- Concerns of acceptability to Ministries versus evidence level on age
- Implications of increased treatment needs (costs/workload) with broader age range

What solutions or ideas are emerging now?

Proposal for age range // voting results:

A. For WLWH, 25-60 years, with need for two negative screens in lifetime for women >60 years // 5
B. Every WLWH >25 years who is sexually active // 1

C. Every WLWH >25 years (need for two negative screens in lifetime for women >60 years) // 3
D. For WLWH 25 – 49 years // 3

Comments:

- How would that (two neg. screens) be recorded? Self-reporting?
- Could it be for WLWH 25 - 49y with need for two negative screens in lifetime
- >49-60 if never screened before at least 1 negative screens in lifetime

Discussion points: key population

What are your concerns regarding the selection of the key population?

Concerns regarding the selection of key population:

- Possibility of including women who have had no visit in the index year in the denominator
- Why limit to current year in care, for a screening parameter that is q3y
- Follow up should be easy
- Including women in the denominator who have no chance of being in the numerator
- Definition of what enrolled in care (in care) means e.g. single visit for care or enrolled in care at a particular clinic or enrolled in care elsewhere

What solutions or ideas are emerging now?

Proposals for the definition of key population:

- Ensure that everyone included in the denominator had a chance to be included in the numerator (i.e. had at least one HIV clinic visit during the period of interest)
- I would suggest we add time period for which to measure the indicator
- And countries can add specific age range they are prioritizing if allowed

Satellite Session 2

Date: Monday, 15th of June, 2021

Time: 15:00 – 17:00 CEST time

Aim of the session

Discuss and agree on definitions for:

- Target population for HPV vaccination indicator
- Age range for HPV vaccination indicator

– Discussion points: Target population for HPV vaccination indicator

Results from the 1st Satellite Session:

– Key population of women: women living with HIV/AIDS who are enrolled in HIV/AIDS care and had at least one HIV clinic visit during the period of interest

– *Is this applicable to define target population for girls for HPV vaccination?*

Note: girls living with HIV/AIDS enrolled in HIV/AIDS Care

Our concerns regarding the definition of target population (girls):

- How capture the information on HPV vaccine among HIV girls who access to vaccine at school?
- Specify the age
- Girls aged 9 to 14
- Girls are mostly vaccinated in schools. How do we make the link to the clinics?
- We mostly receive adolescents and young women
- Only girls living with HIV?
- There could be a simpler age range definition e.g. girls leaving primary school to secondary/high school?
- We will underestimate the true number of girls living with HIV. Use other data sources?
- Define age group
- What is the definition of “enrolled” - does it vary by clinic?
- Define age group/stratification

Proposals for target population (HPV vaccination indicator) // voting results:

A. All preteen girls living with HIV in care at the ART clinic (Age range 9-14) // 0
B. Girls living with HIV in care with at least one visit during the last 12 months (with a proof, not a simple report) // 6
C. Girls living with HIV, seen at least once, and with certain level of validity of information (e.g. vaccination card) if they could provide their vaccination record card or any written proof (instead of only orally reported vaccination received yes/no) // 4
D. Girls aged 15 years who attended at least one visit at an HIV clinic // 5

Comments:

- Is it enough if a girl attended the facility once?
- Once in a life time or in active care?
- That is exactly it - data can't be captured and you can't refer if you don't see the girl within a year
- It is unlikely that if a girl visits a clinic only once she will receive HPV vaccine
- If you limit it to 12 months you will be missing girls
- That's possible in our context where vaccination approach is mainly school-based
- I think that the comparability between countries will be better if we use "girls in care who visited HIV clinic during the year". Better also to monitor a Programme years after years; I mean "with at least one visit during the last 12 months"
- The issue of proof of school vaccination when girls come to the clinic self-reporting being vaccinated is raised
- It is possible in situation where the vaccines are only provided at school
- A vaccination card (or another proof of vaccination) seems an important part of the definition of the target population since most programs in SSA are school-based and girls living with HIV will come for care
- Whilst "PROOF" of vaccination is a very valid concern, the reality is that it is difficult to obtain in many clinical settings (vaccination cards may not exist, may not have been kept, nor remembered to be brought to consultations, even if there is a good way to remind people to try and bring them)

<u>Discussion points: age range for HPV vaccination indicator</u>

Our concerns regarding the selection of age range:

- There is a risk of missing some girls if there is a specific age range fixed. Probably not very practical but (e.g. Vaccination was initiated in Tanzania in 2018. Many girls unvaccinated and beyond the ‘prescribed’ age)
- What is the objective? Calculate incidence or prevalence of vaccination?
- There is a difference between the age ranges in which the information is collected (which can be wide), and how it is going to be reported upon (e.g. percentage of girls vaccinated by 15 years)
- Target age for vaccination varies across countries - use a wider age range to capture different target ages?
- Include girls who are still to be vaccinated, or girls who should have been vaccinated already?

Proposals for age range:

- 9-15 year-old girls living with HIV (choice of 15, based on WHO guidelines) (with at least one visit at the ART clinic)
- Age range 9 - 14 years with the ability to disaggregate by age (ideally there would be the ability to capture a catch-up program for a later age group should it be established that girls have not been reached at school)
- 9 - 14 years old
- Enfant de sexe feminin, entre 9 et 14 ans VIH Positif suivis dans le centre participant
- 9-14 years old to collect. Report on birth cohorts at 15 years
- Our group actually considered that ta wider age range may be beneficial with the option to disaggregate

Satellite Session 3

Date: Monday, 17th of June, 2021

Time: 09:00 – 11:00 CEST time

Aim of the session

- Discuss results from 2nd Delphi round
- Treatment of precancerous lesions
- Treatment of cervical cancer

Discussion points: treatment of cervical precancer

At HIV facility level, is it feasible to document and report this data? What are your concerns/challenges?

Our concerns regarding the documentation and reporting of the data:

- Lack of knowledge of HIV staff on CC prevention
- Screening is done in most cases out of the HIV clinic and treatment done off site. It is therefore challenging to get this data recorded in the HIV clinics
- Register effective treatment for women referred offside is challenging…
- Even on-sight screening has a challenge of documentation and handing over information from one caregiver to another
- Register quality, often not filled properly
- Additional workload of health staff

What solutions or ideas are emerging now?

Ideas and suggestions for treatment of cervical precancer:

- A template for reporting should be available for better coordination across countries
- Registers to be filled need to be simple, 5 items with yes or no answers to not add to much workload for health staff
- Using m-health based approach (phone call) to make sure women referred in other sites have treatment
- Data should be entered offline and online
- The back referral paper (already implemented in some context) should be effectively fulfilled by treatment provider in sites…
- Counsellors to accompany women for offsite treatment and follow-up visits ensured through link to community health workers
- Important to use a unique ID (HIV ID) for a better linkage…
- Counsellors could link women from HIV clinic to screening units
- Secretaries could work in the screening rooms to record data
- Digitalize patient files, digital cervicography
- Avoid referrals when possible

- Referral sites should have all equipment needed for treatment to avoid losing even more women and hence data
- Nurses could follow up women referred through phone calls for example ensuring they received treatment
- Use unique patient identifier or health ID (it can be a national ID) to be used at every encounter with the health care system

Discussion points: treatment of cervical cancer

Indicator: % of women living with HIV/AIDS enrolled in HIV Care diagnosed with invasive cervical cancer appropriately treated or managed by stage of disease according to clinical guidelines

How could this indicator be simplified?

Concerns regarding this indicator:

- "Appropriately" is complex because clinical guidelines are not followed in most countries, there is adaptation according to available resources
- Use of clinical guidelines not known by all specialists
- Quality of pathology and treatment
- Treatment information not available in HIV clinic
- Stage at diagnosis and stage at treatment changes due to long waiting times, treatment information only available at Oncology/Radiation centre and not at the HIV clinic
- HIV staff might not know about cervical cancer treatment and stage-specific guidelines…
- Most screening in clinics is done by nurses who do not necessarily have expertise on staging
- Treatment could be stratified to medical, surgical and palliative
- This information should be collected from the Radiation/treatment centre
- Percentages of women living with HIV diagnosed and managed with type of treatment and diagnosis
- Stage?

How could a simplified indicator be formulated? // voting results

A. Numerator: % Women living with HIV received radiation care / surgery / chemotherapy; Denominator: Women living with HIV with cervical cancer // 0
B. % of women living with HIV/AIDS enrolled in HIV Care diagnosed with invasive cervical cancer and initiate a treatment (stratified by treatment type) // 6

C. % of women enrolled in HIV care diagnosed… who started a treatment (with a time frame?) / who entered into care (appropriateness of the treatment is not taken into account)... // 0

Satellite Session 4

Date: Monday, 17th of June, 2021

Time: 15:00 – 17:00 CEST time

Aim of the session

Discuss and agree on definitions for

- Triage Indicators (core indicators)
- Targets and benchmarks

Discussion points: triage indicators

What concerns and challenges do you see regarding the documentation and reporting of the core triage indicators at HIV facility level?

Received triage examination: % of screen-positive women living with HIV/AIDS enrolled in HIV Care who received a triage examination in a 12 months period

Triage examination positivity rate: % of screen-positive women living with HIV/AIDS enrolled in HIV Care with a positive triage examination result in a 12 months period

Concerns and challenges:

- Lost to follow-up after VIA (treatment on site not always possible)
- Availability of trained specialists (Gyneco) on site
- Challenges in access to available and reliable devices (colposcopy)
- Technical challenges experienced with HPV genotyping (partial genotyping for triage purpose)
- Need to apply standardization for data collection, must use terminologies. Need clear guidance on data systems, training, data aggregation, quality assurance protocols
- Availability of reliable data collection tools
- When HPV is not the first test… if VIA is the first test, then what is the triage?
- Loss to follow-up
- Infrastructure for obtaining referral information often missing -Obtaining results of the triage test (patient reported? reliability)
- With VIA no concerns regarding triage but concerns with test accuracy
- concern for the word triage (different approaches and definitions), loss to follow-up, silo between HIV and cervical cancer screening clinic making data collection a problem at times, HPV is not always available and cost issues, turnover of staff and retraining of triage definitions and data collection

- Does the 12-months period start at screening for each woman, or is it a given 12-months period (e.g., calendar year)?
- This may be completely on the other side. Triage is not necessarily common practice in HIV clinics in these settings except within research projects. When present, this may add to the workload of the already 'over-burdened' staff so collecting this data may even be more challenging (not in any way refuting the importance of triage, just concerns about feasibility)
- Would all screening/triage methods be combined in one indicator? Or would the indicator be stratified by approach?
- How will screening positivity be defined (cut-offs)?
- Le défi majeur est la faisabilité dans la mesure où cela pourrait retarder le traitement avec le risque de louper des patients >> The major challenge is feasibility as this could delay treatment with the risk of missing patients

What can you do to advance the monitoring of triage? What do you need for this?

What we can do:

- … Sensitize/inform personnel in charge of reporting
- Enhance women acceptability of triage procedures
- Update data on cervical cancer screening collection tools to include triage information in sites…
- Better identification of women (unique ID)…
- Unique client IDs…
- Update data collection tools (include triage testing)…
- Define the scope of the implementation (IeDEA sites? A country? A region?)
- Identify groups that have successfully collected these data and learn from them
- Enforce an absolutely minimal dataset for data collection (no "nice to have" variables)

What we need:

- Good and standardized tools for monitoring…
- …Coordination with national cancer programs in participating countries
- …Better collaboration gynecological units and cancer units
- Centralized electronic data systems with unique identifiers (too ambitious?)…
- Testing platforms (GeneXpert) and train staff to use them…
- Education to health care providers
- Register
- Gaps in continuity due to interrupted funding
- Peer educators, and community workers to ensure follow-up
- Training of health care workers on the importance of collecting the requested data

- Funding
- Government approval for this data collection (integration into data systems, use of clinician/administrator time to support the data collection, incentives)
- ...Support from policy makers
- Systems for data collection (depends on scope), methods for data aggregation, dealing with missingness, quality control. A formal process for reviewing and modifying the data collection over time
- better definition and triaging based on different groups/institutions
- more trained providers for treatment (no reason for screening or triaging if no effective treatment)
- facilitators to decrease loss of follow up, person responsible to keep track of data
- need for education and counseling because health literacy on cervical cancer is low in many places

Discussion points: targets and benchmarks

At IeDEA level, we suggest to not define targets and benchmarks for the Cervical Cancer Prevention and Care Cascade Indicators.

What arguments do you see for using targets and benchmarks for IeDEA Cascade indicators?

Arguments for using targets and benchmarks for IeDEA Cascade indicators:

- Needed for evaluation and training…
- To reinforce sensitization in facilities
- If IeDEA sites were to collect this data in the DES format, it could be submitted to the Harmonist Toolkit and automatic scripts could calculate these metrics and produce downloadable PDF reports

Comments:

- Need of monitoring to measure the time trends, to give objectives to health providers, data collection is important+++, data collection is challenging to implement in the field
- IeDEA is not always in the best position to collect data and dependent on clinics. IeDEA needs more advocacy to get these data. The Ministry needs to put these benchmarks as necessary for cervical cancer programs particularly in HIV women. There is an issue of paper vs electronic records and capability
- Funding streams at each institution is different so fulfilling the benchmarks may not be uniform

What arguments do you see against using them?

Arguments against using targets and benchmarks for IeDEA Cascade indicators:

- Needed to be adapted according to countries

- Need to contextualize benchmarks
- Need to run a site assessment at local level
- Don't have the necessary data. Scope is too broad (all of IeDEA). No plan or funding for this data collection
- Too many site/country customizations needed to interpret data
- No regional/country support for this and it can be complicated to obtain (need to engage leadership at each site, see experience with IeDEA Dashboard)
- IeDEA doesn't have a mandate to set benchmarks/targets for countries. Our sites are not sufficiently representative of their countries (for many regions). We should work with WHO or other groups

Impressions: Do you agree that we won't define targets and benchmarks for the IeDEA cascade indicators? Yes or No?

YES: 7 votes

NO: 4 votes

The Virtual Stakeholder Meeting 2021

Date: Monday, 24th of June, 2021

Time: 14:00 – 17:00 CEST time

Agenda

The Cervical Cancer Prevention and Care Cascade for women living with HIV in sub-Saharan Africa by PD Dr Julia Bohlius, Swiss Tropical and Public Health Institute

A facility-based survey of cervical cancer prevention and control programs in sub-Saharan Africa by Serra Asangbeh, PhD student, University of Bern and Swiss Tropical and Public Health Institute

Developing indicators to measure health care performance by Prof. Dr David Schwappach, MPH, Director, Swiss Patient Safety Foundation

Cervical cancer screening for women living with HIV – the challenges and evidence gaps by Dr Partha Basu, Deputy Head, Early Detection, Prevention and Infections Branch, IARC/WHO

Case reports from the region:

- Advancing Cervical Cancer Screening in HIV-positive Women by Anjali Sharma, CIDRZ
- Newlands Cascade onsite VIA retrospective cohort study by Dr Katayoun Taghavi
- Mozambique Cascade by Idiovino Rafael, Programme Manager Mozambique, SolidarMed
- Newlands HPV screening strategy by Dr Margaret Pascoe, Medical Director of Newlands Clinic, Zimbabwe

Indicator Integration into IeDEA-DES by Beverly Musick, Regional Data Manager IeDEA East Africa and Prof. Dr Stephany Duda, Associate Professor of Biomedical Informatics, USA

Summary of lectures

The Cervical Cancer Prevention and Care Cascade for women living with HIV in sub-Saharan Africa by PD Dr Julia Bohlius, Swiss Tropical and Public Health Institute

- The project has aim to develop internationally agreed-upon indicators to monitor provision of cervical cancer care to women living with HIV in sub-Saharan Africa throughout consensus process with stakeholders from this region.

A facility-based survey of cervical cancer prevention and control programs in sub-Saharan Africa by Serra Asangbeh, University of Bern and Swiss Tropical and Public Health Institute

- The preliminary results from a facility-based survey of cervical cancer prevention and control programs in sub-Saharan Africa are presented. Main findings: HPV vaccination is available in less than half of the participating sites; funding support for cervical

screening is rare; diagnostic and treatment services are mostly centralized (women often referred for these services off-site); cost is a barrier to diagnosis and treatment in most sites; data collection systems are available for HIV but rare for CC prevention; and across the cascade, data availability greatly reduces from screening to follow-up of treated women and women initially screened negative.

Developing indicators to measure health care performance by Prof. Dr David Schwappach, Swiss Patient Safety Foundation

- To develop indicators to measure health care performance, it is important to: accept the pain of reduction a complex world to simple metrics; mind the consequences adaption to indicators may have; resist to make indicators overly complex; and choose sensitive-to-differences indicators and take a learning-oriented process

Cervical cancer screening for women living with HIV – the challenges and evidence gaps by Dr Partha Basu, IARC/WHO

- Cervical cancer in women living with HIV, screening of women living with HIV and management of cancer, and evidence gaps in screening and management has been presented. There are still many questions that should be addressed in future regarding ideal screening interval, primary and triage test for women living with HIV.

Advancing Cervical Cancer Screening in HIV-positive Women by Anjali Sharma, CIDRZ

- The aim of this research was to explore facilitators and barriers to providing CC care from women's and healthcare provider perspectives in order to reduce incidence of CC through improved service delivery and update in Zambia. Gaps that have been identified: poor referral and follow up systems of patients; poor integration of ART and cervical cancer clinics; lack of access to funds to the facility on samples to be tested; long waiting times for results after biopsy; lack of correct information on cervical cancer.

Cervical cancer screening cascade at Newlands Clinic by Dr Katayoun Taghavi, University of Bern, Switzerland

- This retrospective cohort study had aim to define and assess a cervical cancer screening cascade for women living with HIV enrolled at an ART clinic in Zimbabwe and to explore patient factors associated with retention through stages of the cascade. Main findings: Analysing outcomes along the proposed cervical screening cascade can identify areas for improvement; interventions are needed to improve linkage to treatment for screen-positive women who do not qualify for same-day cryotherapy; and many women continued to screen positive after treatment.

Cervical Cancer Prevention following a cascade strategy: successes and challenges by Idiovino Rafael, Mozambique SolidarMed

- The aim of this project has been to improve women's access to cervical cancer prevention and care following a cascade strategy in Northern Mozambique. Results to date> one dedicate examination room for VIA has been established; biopsies are possible now with analysis in Nampula; and LEEP is available on site now (equipment, health worker trained). Some challenges that should be addressed in future: what happen after 2nd referral? Can having an examination room integrated inside the HIV clinic improve screening and treatment uptake?

Cervical Cancer Screening at Newlands Clinic by Dr Margaret Pascoe, Newlands Clinic, Zimbabwe

- Performance of cervical cancer screening at Newlands Clinic has been presented. In total, 1330 HPV tests has been performed (51% were HPV positive). Of these who has been HPV positive; 46% has been tested with VIAC (20% has been VIAC positive).

An End-to-End Simple Record Linkage Tool by Mwansa Lumpa, CIDRZ Zambia

- Advantages and disadvantages of record linkage method has been presented, and a framework for efficient record linkage (e2elink) and its implementation has been described.

Indicator Integration into IeDEA-DES by Beverly Musick, IeDEA East Africa and Prof. Dr Stephany Duda, USA

- IeDEA Data Exchange Standard (IeDEA DES) and integration of cervical cancer indicators into IeDEA DES has been presented.

Discussion

*Questions for lecturer Dr Partha Basu, Deputy Head, Early Detection, Prevention and Infections Branch, IARC/WHO, after presentation: Cervical cancer screening for women living with HIV – the challenges and evidence gaps**

- What drives the recommendation of 50 years as the upper age limit
- Genexpert costs are high. For rural areas sample transport to a facility able to do the test is required and the results tend to come late or never. Are there any Point-of-care tests being developed?
- We were wondering about the long term outcomes of women who had prophylactic ablation of the TZ. Is there data?
- Quelles sont les recommandations pour le dépistage après 50 ans d'autant plus que les PvVIH vieillissent beaucoup plus dans les soins? / What are the recommendations for testing after age 50, especially as WLHIV age much more in care?
- How young are women when prophylactic cauterization is done? What are adverse effects, especially for pregnancy and birthing

- What will be your comment on the HIV disease control in the HPV testing interval decisions specifically for HPV negative and uncontrolled HIV disease?

Response by Partha Basu: Women with poorly controlled HIV or those not receiving ART have even higher risk of cervical cancer. VIA screening can be repeated after 1 year for them. It may not be feasible to screen them with HPV test too frequently. 3 years will be a reasonable interval for HPV test

- Should recommendations be different for vertically infected girls/women (infected with HIV and HPV from birth), esp lower age recommendation
- One of the limiting factors in Zambia is the cost of the HPV test kits. without partner support, it may be difficult to expand and sustain. Are we expecting negotiated prices for LMIC?

Response by Partha Basu: WHO is trying to engage the manufacturers to reduce the cost. Hope things will change as the demand increases

- Most studies consistently shows that treatment outcome among HIV patient is poor compare to Negative (recurrence). Don't you think it is because we are using same treatment criteria for two different population?

Response by Partha Basu: That is another problem. Using HPV test as the test of cure has a major limitation in WLHIV. In our Zambian study we find that 60% women are HPV +ve even after treatment. However, some of the studies showing low cure rates have used histopathology as the endpoint.

- What about girls with perinatally acquired HIV infection with early sexual debut?(sometimes as young as 10 years old in some communities). Is 25 years not late?
- I also appreciate the use of HPV testing as a response to Eliminate CC, but with the low return rate for the HPV positives especially in Zambia, the purpose is defeated and we would rather stick to VIA as a screen and treat
- Quel est votre avis sur l'autoprélèvement versus prélèvement fait par le prestataire dans le cadre du dépistage avec le test HPV / What is your opinion on self-collection versus provider-collection for HPV testing

Response by Partha Basu: Self-collection has a huge potential of improving coverage in the LMICs. Most studies in LMICs have shown high acceptance of self-collection. That will be way forward in post-covid days

- What is WHO guide for women who are HPV positive and VIA negative upon triage?

Response by Partha Basu: HPV positive VIA negative women should be recalled for HPV test after 1 year

- How much cost one HPV test kit in Zambia?

Response by other participant: Am not sure about the cost of the HIV test kit but for the HPV, It goes as high at $16.99 per test kit without collection and effort

- I am delighted with the lowering of the age range for screening. We see anogenital cancers in young vertically infected women

**Some questions has been addressed orally during the discussion and are not presented in this report.*

Reflecting on the meeting

What opportunities and ideas do you see opening up?

- Strengthening Integration of HIV and CC
- Our group was very impressed by the programs but we discussed the resources needed to have a successful program. Even if we had the technical and SOPs of the successful programs, we may not have the necessary financial support from the institution without grant funding which is not sustainable in the long run
- Opportunities and ideas, not sure. We discussed again about HPV and how it seems challenging to implement
- Having a clear client flow in HIV clinic that ensures women screen as well for CC
- From Geraldine and Miranda (community members): They related quite well with the findings from the qualitative study. Cost is a huge barrier. sometimes you have the money but there are no treatment platforms available
- Communicating the cervical cancer prevention message in a way that the community can understand is very important and the stories of beneficiaries will play great role
- We need to improve women awareness on importance of early CC screening. Health care workers need also be empowered on CC screening. We need to improve access to CC screening
- HPV testing in controlled settings and places were the women visit routinely such as prisons, churches, schools, universities
- Our group focused on giving relevant messages to women to advocate for CCS. Dispelling myths is important
- Interesting reports from Newland clinics. They pointed out the need of a deep analysis for implementing the best test (or combination of test) to ascertain cure after treatment given the high rate of recurrence
- We need to ensure that women fully understand the whole process of CC screening. Let's empower the women for better results
- Educating the women why they need to come to be screened and to comeback as instructed by the healthcare worker. This will require that healthcare workers are able to clearly explain to women why this screening and treatment is necessary

- Male partners/men need to understand too, especially when it comes to treatment and sexual abstinence
- We need to get men on board! Many women are not empowered to access services without their husband's permission

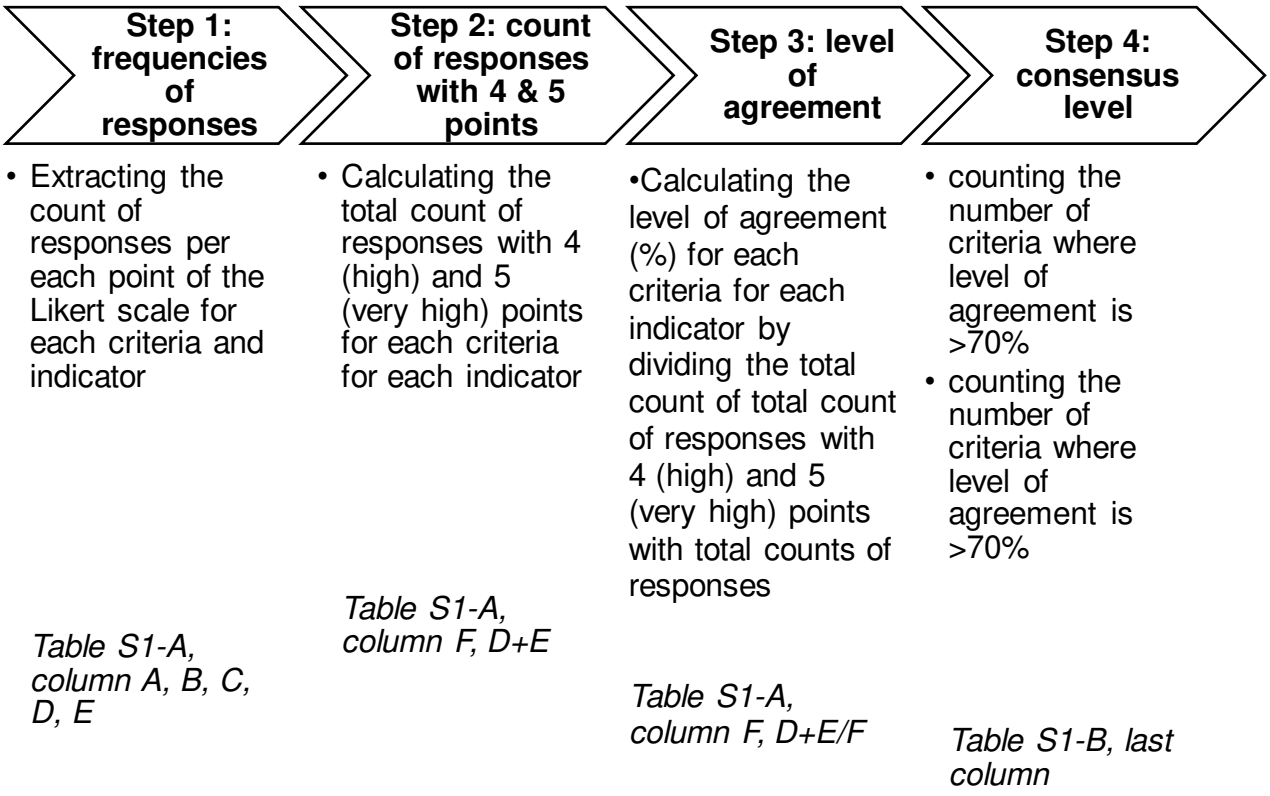
Online resources

All recordings from the Virtual Stakeholder Meeting are available here:

File S4: Quantitative analysis

Rating calculation

Rating calculation was performed using Excel. We calculated frequencies of responses for each point of Likert Scale (1 – very low, 5 – very high) per criteria and indicator (Step 1). We summed frequencies of responses with 4 (high) and 5 (very high) points per criteria and indicator (Step 2). We then calculated percentage of frequency responses with 4 (high) and 5 (very high) points within the same criteria and indicator (level of agreement, Step 3). Afterward, we highlighted indicators that had high level of agreement (more than 70%) within the criteria and indicator (Step 4), and indicators that reached consensus by having high level of agreement in three or more criteria (Step 5). We utilized this process for both results from Round 2 and 3, and presented them in a heat map, ordered by highest to lowest numbers in Round 3, followed by the highest to lowest numbers in Round 2. The calculation or rating results is summarized in Figure S1 and Table S1.



File S4 Figure S1. *Calculation process of rating results*

File S4 Table S1. *Calculation process of rating results: an example; A) steps 1-3, B) step 4.*

A: Step 1. Step 2, Step 3 and Step 4							
Indicator & Criteria	Likert Scale points and individual responses						
Variable	1 (very low) (A)	2 (low) (B)	3 (medium) (C)	4 (high) (D)	5 (very high) (E)	Total (F=A+B+C+D+E)	LA (%) (D+E / F) * 100
Indicator 1*							
Relevance	0	0	3	24	18	45	93%
Feasibility	0	12	13	12	8	45	44%
Comparability	0	5	8	20	12	45	71%
Reliability	0	6	13	16	10	45	58%
Understandability	0	1	3	26	15	45	91%
Indicator 2...							

B: Step 4						
Indicator (Ind)	Relevance	Feasibility	Comparability	Reliability	Understandability	# of criteria with high LA (>70%)
Ind. 1	LA (%)	LA (%)	LA (%)	LA (%)	LA (%)	e.g. 5**
Ind. 2	LA (%)	LA (%)	LA (%)	LA (%)	LA (%)	e.g. 4**
Ind. 3	LA (%)	LA (%)	LA (%)	LA (%)	LA (%)	e.g. 2
..						

*Numbers represent results from Round 3 for the indicator: Rescreened within Recommened Screening Interval; **highlighted if ≥3; Abbreviations: LA – Level of agreement (%), # – number, e.g. – for example.

Ranking calculation

Participants rated indicators per domains by importance. We ranked indicators based on the ranking score (RS). To determine RS for each indicator, we first calculated frequency (how many respondents placed an indicator as 1st, 2nd, 3rd etc., within each domain) (Step 1). We then multiplied frequencies by the weight (W) of the ranked position: first place had highest value (Wmax) and last place had lowest value (Wmin): RS = x1W1+x2W2+x3W3+x4W4…

where x is the frequency (response count) of participants who ranked the indicator at the first place, and W is the weight of the ranked position)(Step 2). The weight of the ranked position depended by the number of indicators (and consequently the number

of potential positions) within domain (e.g. if one domain contained 3 indicators that has been ranked, then W ranged from 1(Wmin) to 3 (Wmax) (Step 3). For example, an indicator can be ranked as 1st by 10 participants, as 2nd by 20 participants and as 3rd by 30 participants. The ranking score is then: RS =10×3+20×2+30×1. To calculate the appropriate rank in each domain, we used excel function RANK.AVG. This function assigns a rank to a given value based on its relative position among other values in the selected field. We applied this method only on indicators that reached consensus in Round 3. The calculation or rating results is described in Table S2.

File S4 Table S2. Calculation process of ranking results: an example

Indicator	**# of participants ranking indicator at:**				**Ranking Score (RS)**	**Overall Rank Position**
	1st place	**2nd place**	**3rd place**	**4th place**		
	Rank 1 (R1)	**Rank 2 (R2)**	**Rank 3 (R3)**	**Rank 4 (R4)**		
Weight	W4 (4)	W3 (3)	W2 (2)	W1 (1)	R1*4+R2*3+R3*2+R4*1	
Indicator 1	41	4	0	0	176	1
Indicator 2	2	18	18	7	105	3
Indicator 3	2	21	18	4	111	2
Indicator 4	0	2	9	34	58	4

The highest RS=1st rank, the lowest RS=4th rank

File S5: Qualitative analysis of the feedback

In all rounds, participants were able to provide feedback on each indicator using an open text box at the end of the survey's page. After each round, we summarized feedback for each indicator and shared a report with participants in the subsequent rounds.

Preliminary analysis

We conducted preliminary analysis of comments after Round 2 and before satellite meetings to define topics for further discussion. These topics were further implemented in satellite meetings' agenda. We developed questions for discussions that followed each topic with an aim to harvest ideas how to improve indicators and their utilization. This is the overview of topics discussed and questions for discussion:

Satellite session 1:

- Age range for screening in women living with HIV
  - *What are your concerns regarding the selection of age range?*
  - *What solutions or ideas are emerging now?*
- Key population
  - *What are your concerns regarding the selection of the key population?*
  - *What solutions or ideas are emerging now?*

Satellite session 2:

- Target population for HPV vaccination indicator
  - *Is this applicable to define target population for girls for HPV vaccination?*
  - *Proposals for target population (HPV vaccination indicator)*
- Age range for HPV vaccination indicator
  - *Proposals for age range*

Satellite session 3:

- Discuss results from 2nd Delphi round
- Treatment of precancerous lesions
  - *At HIV facility level, is it feasible to document and report this data? What are your concerns/challenges?*
  - *What solutions or ideas are emerging now?*
- Treatment of cervical cancer
  - *How could this indicator be simplified?*

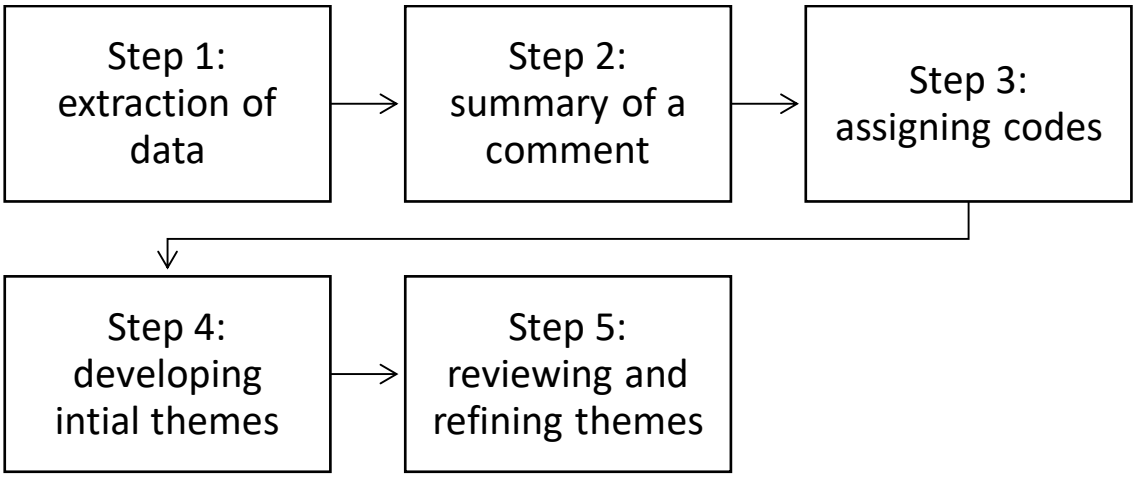
- *How could a simplified indicator be formulated?*

Satellite session 4:

- Triage Indicators (core indicators)
  - *What concerns and challenges do you see regarding the documentation and reporting of the core triage indicators at HIV facility level?*
  - *What can you do to advance the monitoring of triage? What do you need for this?*
- Targets and benchmarks
  - *What arguments do you see for using targets and benchmarks for IeDEA Cascade indicators?*
  - *What arguments do you see against using them?*

Thematic analysis

Two researchers (JB and MD) conducted qualitative analysis of feedback provided in all rounds using the reflexive thematic analysis with inductive approach. We chose thematic analysis to explore potential patterns in participants' feedback [1, 2]. Inductive approach refers to the process of deriving meaning and creating themes from the data without any preconceptions. Reflexive analysis means we changed, removed, or added codes as we worked through the data. In summary, we firstly extracted all comments from open box questions from all three rounds (step 1). Comments that were in French we translated in English using online DeepL translator. Then we summarized each comment (step 2) and we assigned codes (step 3). Firstly, we generated initial themes, and after we reviewed and refined assigned themes (step 4 and 5). We used Excel form to perform this analysis. The Excel file with depersonalized information is available upon reasonable request from the corresponding author.



File S5 Figure S1. *Summary of thematic analysis*

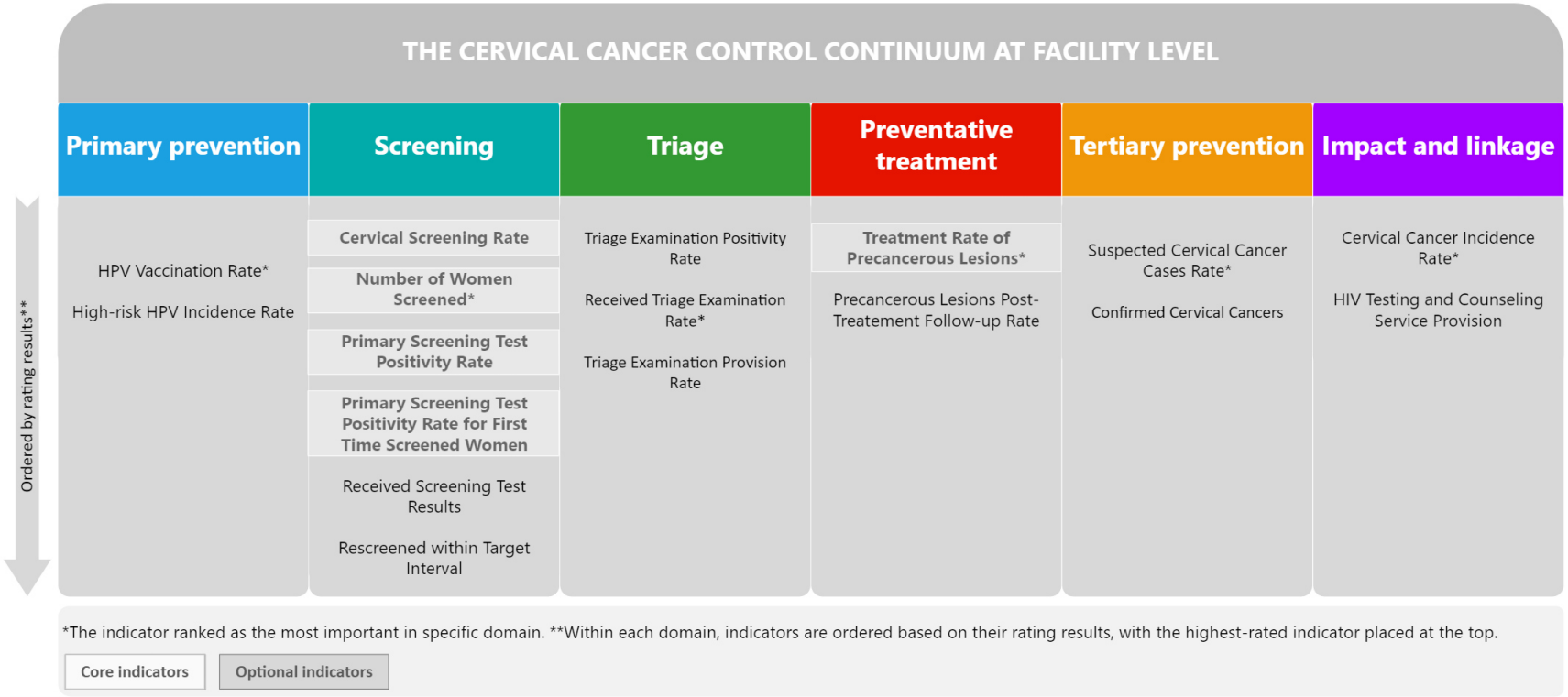
References

1. Byrne D. A worked example of Braun and Clarke's approach to reflexive thematic analysis. *Qual Quant* **56**, 1391–1412 (2022).
2. Maguire M & Delahunt B. Doing a Thematic Analysis: A Practical, Step-by-Step Guide for Learning and Teaching Scholars. AISHE-J, 9, 3351. (2017).

File S6: The final list of indicators that reached consensus & relevant information

Overview of core, optional and 1st-ranked indicators per domains that reached consensus

The overview of core, optional and 1st-ranked indicators per domains that reached consensus in round 3. Consensus is reached if the indicator had a high level of agreement (>70% of respondents rated an indicator as 4 and 5 points on Likert scale) in ≥3 criteria. Within each domain, indicators are ordered based on their rating results, with the highest-rated indicator placed at the top. Indicators that reached a high level of agreement in all five criteria we labelled as core indicators, and those with a high level of agreement in three or four criteria as optional indicators. The indicator ranked as the most important in each domain is marked with *.



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Tables of indicators that reached consensus in Round 3

Next chapter lists tables of indicators that reached consensus in round 3. We listed first tables of indicators that reached consensus in all five criteria (core indicators: 'Cervical Screening Rate', 'Number of Women Screened for Cervical Pre-cancer', 'Screening Test Positivity Rate', 'Screening Test Positivity Rate for First Time Screened Women', and 'Treatment Rate of Precancerous Lesions'). Afterward we listed indicators following domains and the order of highest rated indicators in that domain.

Core indicators

Title	NUMBER OF WOMEN SCREENED FOR CERVICAL PRE-CANCER
Definition	Number of screened "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest"
Numerator	Total number of "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" screened in a 12-month period
Denominator	Not applicable
Calculation	numerator
Purpose and rationale	Purpose: to understand and estimate the demand for screening services. Rationale: to meet the demand for cervical pre-cancer screening and treatment needs, this number can be used to forecasting and planning required resources.
Data source	Main source: patient records at HIV clinic If data are not available from patient records at the HIV clinic, they might be obtained from: • Health information systems • Dedicated projects
Frequency	At program level: according to local need, at IeDEA level: annually
Disaggregation	• by age group or range • by screening visit type • by screening method of precancerous lesions You can find more information about disaggregation below (paragraph: indicator disaggregation).
Data guidelines	This indicator should be calculated for a 12-month period. However, if other time periods are required by local program needs, the definition of the given time period can be adjusted.
Additional comments	This number is most useful for facilities with nascent systems with limited capacity, or without current capacity to collect more comprehensive data. Otherwise, it does not need to be monitored directly or separately, because it presents components of several other indicators mentioned later. In the interest of simplicity, we do not record women, who are not eligible for screening for medical reasons, such as women who had a hysterectomy with no residual cervix, or women who refused screening, or other reasons.

Title	CERVICAL SCREENING RATE
Definition	Screened “women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest”
Numerator	Number of “women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest” who have been screened with a cervical screening test in a 12-month period
Denominator	Total number of “women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest” in a 12-month period
Calculation	numerator/denominator per 12-month period
Purpose and rationale	Purpose: to monitor the rate of participation in screening at facility level. Rationale: high screening rates will increase the chances that a screening program will have the desired impact on cervical cancer incidence and mortality.
Data source	Main source: patient records at HIV clinic If data are not available from patient records at the HIV clinic, they might be obtained from: • Health information systems • Dedicated projects
Frequency	At program level: according to local needs; e.g. annually, quarterly, monthly; at IeDEA level: annually
Disaggregation	• by age group or range • by screening visit type • by screening method You can find more information about disaggregation below (paragraph: indicator disaggregation).
Data guidelines	This indicator should be calculated for a 12-month period. However, if other time periods are required by local program needs, the definition of the given time period can be adjusted.
Additional comments	In the interest of simplicity, we do not record women, who are not eligible for screening for medical reasons, such as women who had a hysterectomy with no residual cervix, or women who refused screening, or other reasons.

Title	SCREENING TEST POSITIVITY RATE FOR THE PRIMARY SCREENING TEST
Definition	Screened "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" who received a positive primary screening test result in a 6-month period Standardized definition of screening test results are provided below.
Numerator	Number of screened "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" who received a positive primary screening test result in a 6-month period
Denominator	Total number of screened "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" in a 6-month period
Calculation	numerator/denominator per 6-month period
Purpose and rationale	Purpose: to measure the percentage of primary screening test positive results in screened population. Rationale: The screening test positivity rate is one of the three globally standardized performance indicators recommended by WHO as fundamental to monitoring a cervical cancer prevention programs.
Data source	Main source: patient records at HIV clinic If data are not available from patient records at the HIV clinic, they might be obtained from: • Health information systems • Dedicated projects
Frequency	At program level: according to local needs, e.g. annually, quarterly, monthly; at IeDEA level: annually
Disaggregation	• by age group or range • by screening method • by screening visit type You can find more information about disaggregation below (paragraph: indicator disaggregation).
Data guidelines	WHO standardized the terminology for classifying the results of cervical screening tests as follow: VIA results – Negative – Positive, eligible for pre-cancer treatment – Positive, suspected cancer Positive, eligible for pre-cancer treatment, and positive, suspected cancer are both considered as a positive screening result. Women with a positive (eligible for treatment or suspicious for cancer) VIA screening (or triage) test result are therefore considered screen-positive (or triage-positive) for informing this indicator. If the VIA result is inconclusive or indeterminate, the procedure should be repeated or a colleague consulted. When these options are not available, the screening result has to be considered as screen-positive for informing this indicator. Pap smear / cytology – Normal (negative for intraepithelial lesions or malignancy) – Abnormal (any epithelial cell abnormality) Any epithelial cell abnormality is considered as screen-positive for informing this indicator. While it is possible to determine degrees of abnormality and

	even identify precancer from cytology, both precancer and suspected cancer are captured as a positive result. Women with an abnormal result on a Pap smear screening test are therefore considered screen-positive. HPV test results – Negative – Positive – Retest required Women should receive their results as soon as possible within 6 months in order to start appropriate treatment when needed. Therefore, we recommend this indicator to be calculated over a 6-month period.
Additional comments	WHO recommends to use HPV DNA detection as the primary screening test for women living with HIV. When providing HPV DNA testing, WHO suggests using either samples taken by a health-care provider or self-collected samples. In the interest of simplicity, we do not record women, who are not eligible for screening for medical reasons, such as women who had a hysterectomy with no residual cervix, or women who refused screening, or other reasons.

Title	SCREENING TEST POSITIVITY RATE FOR THE PRIMARY SCREENING TEST FOR FIRST TIME SCREENED WOMEN
Definition	The first time screened "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" who received a positive primary screening test result in a 12-month period Standardized definition of screening test results are provided below.
Numerator	Number of the first time screened "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" who received a positive primary screening test result in a 12-month period
Denominator	Total number of the first time screened "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" in a 12-month period
Calculation	numerator/denominator per 12-month period
Purpose and rationale	Purpose: considering only data relevant to first time screenings is a key to estimate whether a screening program is reaching these at higher risk. Rationale: WHO recommends focusing on first time screenings in order to align to the goals of most programs, and because this information is key to reach global WHO targets. The screening test positivity rate is one of the three globally standardized performance indicators recommended by WHO as fundamental to monitoring a cervical cancer prevention programs. This indicator can be derived from an additional disaggregation by screening visit type from the previous indicator (screening test positivity rate for the primary screening test). However, due the importance of reaching the screening naïve population, WHO recommends using this indicator independently.
Data source	Main source: patient records at HIV clinic If data are not available from patient records at the HIV clinic, they might be obtained from: • Health information systems • Dedicated projects
Frequency	At program level: according to local needs, e.g. annually, quarterly, monthly; at IeDEA level: annually
Disaggregation	• by age group or range • by screening method You can find more information about disaggregation below (paragraph: indicator disaggregation).
Data guidelines	WHO standardized the terminology for classifying the results of cervical screening tests as follow: VIA results – Negative – Positive, eligible for pre-cancer treatment – Positive, suspected cancer Positive, eligible for pre-cancer treatment, and positive, suspected cancer are both considered as a positive screening result. Women with a positive (eligible for treatment or suspicious for cancer) VIA screening (or triage) test result are therefore considered screen-positive (or triage-positive) for informing this indicator. If the VIA result is inconclusive or indeterminate, the procedure should be repeated or a colleague consulted. When these options are not

	available, the screening result has to be considered as screen-positive for informing this indicator. Pap smear / cytology – Normal (negative for intraepithelial lesions or malignancy) – Abnormal (any epithelial cell abnormality) Any epithelial cell abnormality is considered as screen-positive for informing this indicator. While it is possible to determine degrees of abnormality and even identify precancer from cytology, both precancer and suspected cancer are captured as a positive result. Women with an abnormal result on a Pap smear screening test are therefore considered screen-positive. HPV test results – Negative – Positive – Retest required This indicator should be calculated for a 12-month period. However, if other time periods are required by local program needs, the definition of the given time period can be adjusted.
Additional comments	WHO recommends to use HPV DNA detection as the primary screening test for women living with HIV. When providing HPV DNA testing, WHO suggests using either samples taken by a health-care provider or self-collected samples. In the interest of simplicity, we do not record women, who are not eligible for screening for medical reasons, such as women who had a hysterectomy with no residual cervix, or women who refused screening, or other reasons.

Title	TREATMENT RATE OF PRECANCEROUS LESIONS
Definition	Screen-positive "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" who have received treatment in a 6-month period In the "screen-and-treat approach", the decision to treat is based on a positive primary screening test. In the "screen, triage and treat approach", the decision to treat is based on a positive primary screening test followed by a positive second test (triage test), with or without histologically confirmed diagnosis. For strategies where the decision of treatment depends on the results of a triage test, this indicator must be adjusted to capture those who are both screen-positive and triage-positive. WHO suggests to treat as soon as possible within six months to reduce the risk of loss to follow-up. Therefore, we recommend this indicator to be calculated over a 6-month period.
Numerator	Number of screen-positive "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" who have received treatment in a 6-month period
Denominator	Number of screen-positive "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" in a 6-month period
Calculation	numerator/denominator per 12-month period
Purpose and rationale	Purpose: to monitor whether all women requiring treatment received treatment. Rationale: WHO defined 90-70-90 targets by 2030 to eliminate cervical cancer globally. One of these targets aims that 90% of women identified with cervical disease are treated.
Data source	Main source: patient records at HIV clinic If data are not available from patient records at the HIV clinic, they might be obtained from: • Health information systems • Dedicated projects • Service delivery data (triage or screening facility)
Frequency	At program level: according to local needs, e.g. annually, quarterly; at IeDEA level: annually
Disaggregation	• by age group or range • by screening (or triage) method • by treatment type for precancerous lesions You can find more information about disaggregation below (paragraph: indicator disaggregation).
Data guidelines	If multiple screening methods or strategies exist at facility level, it is important to accurately monitor whether the women who needed treatment received treatment. For example, VIA can be used both as primary and triage test that follows HPV testing. All women positive at VIA screening need treatment BUT not all women who screen-positive with an HPV Test need treatment – only those who also tested positive on the VIA triage examination need treatment. Therefore, as screen-positive women will be calculated women who screened positive on VIA screening and who screened positives on VIA triage, but not all positives screened with HPV Test. This indicator should be calculated in a 6-month period. However, if other time periods are required by local program needs, the definition of the given time period can be adjusted.
Additional comments	Once a decision to treat a woman is made it is good practice to **treat as soon as possible within six months**. However, in women who are pregnant, good practice includes deferral until after pregnancy. In circumstances when treatment is not provided within this time frame, it is good practice to re-evaluate the woman before treatment.

Optional indicators

Primary prevention

Title	HPV VACCINATION RATE
Definition	HPV vaccinated “girls living with HIV enrolled in care with at least one HIV clinic visit during the period of interest” aged 9-14 years
Numerator	Number of “girls living with HIV in care with at least one HIV clinic visit during the period of interest” aged 9-14 years who are fully immunized (received all doses defined by program) with HPV vaccine in a 12-month period
Denominator	Total number of “girls living with HIV in care with at least one HIV clinic visit during the period of interest” aged 9-14 years in a 12-month period
Calculation	numerator/denominator per 12-month period
Purpose and rationale	Purpose: to monitor the vaccination progress in girls living with HIV receiving care at HIV clinics. Rationale: WHO defined 90-70-90 targets by 2030 to eliminate cervical cancer globally: 90% of girls are fully vaccinated by the age of 15 years. WHO’s current guidelines recommend that young adolescent girls receive two doses of vaccine to be fully protected.
Data source	Main source: patient records at HIV clinic If data are not available from patient records at the HIV clinic, they might be obtained from: • Health information systems • Dedicated projects
Frequency	At program level: according to local needs, at IeDEA level: annually
Disaggregation	• by age group or range • by level of immunization • by number of doses • by vaccine type You can find more information about disaggregation below (paragraph: indicator disaggregation).
Data guidelines	This specific indicator collects data on girls only. If vaccination data are recorded, the source of information (orally reported only or vaccination record provided) should be recorded as well. According to local circumstances, it can also assess the number of boys vaccinated against HPV, and in that case, the definition of the indicator should be adapted accordingly. This indicator should be calculated for a 12-month period. However, if other time periods are required by local program needs, the definition of the given time period can be adjusted.
Additional comments	This indicator can be a first important step towards evaluating the HPV vaccine distribution in girls living with HIV and receiving care at HIV care and treatment sites. Some sites may not conduct HPV vaccinations and therefore it may be challenging to obtain data for HPV vaccine status. Some sites may also not record data on HPV vaccination status. In the interest of simplicity, reasons for non vaccination (e.g. stock outs, refusal, contraindications etc.) will not be recorded.

Title	HIGH-RISK HPV AGE-SPECIFIC INCIDENCE RATE
Definition	Newly diagnosed high-risk HPV cases among “girls and women living with HIV/AIDS enrolled in care with at least one HIV clinic visit during the period of interest” in a specific age range in a 12-month period
Numerator	Number of new high-risk HPV cases diagnosed among “girls and/ women living with HIV/AIDS enrolled in care with at least one HIV clinic visit during the period of interest” in a specific age range in a 12-month period
Denominator	Total number of “girls and women living with HIV/AIDS enrolled in care with at least one HIV clinic visit during the period of interest” in s specific age range screened for high-risk HPV in a 12-month period
Calculation	numerator/denominator per 12-month period
Purpose and rationale	Purpose: to measure newly occurring high-risk HPV infections. Rationale: high-risk HPV infections are the primary cause of precancerous and cancerous cervical lesions.
Data source	Main source: patient records at HIV clinic If data are not available from patient records at the HIV clinic, they might be obtained from: • Health information systems • Dedicated projects
Frequency	At program level: according to local needs, at IeDEA level: annually
Disaggregation	• by age group or range • by HPV subtype You can find more information about disaggregation below (paragraph: indicator disaggregation).
Data guidelines	This indicator can be used to assess the impact of HPV vaccination programs. This indicator should always include a specific age-range or group in its definition. This indicator should be calculated for a 12-month period. However, if other time periods are required by local program needs, the definition of the given time period can be adjusted.
Additional comments	This indicator captures only infections with HPV high-risk subtypes.

Secondary prevention - screening

Title	RECEIVED SCREENING TEST RESULTS
Definition	"Women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" who received their screening test results in a 6-month period
Numerator	Number of "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" who received their screening test results in a 6-month period
Denominator	Total number of "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" with a screening test result in a 6-month period
Calculation	numerator/denominator per 6-months period
Purpose and rationale	Purpose: to monitor if women living with HIV who have been screened receive screening test results. Rationale: women who are screened with screening methods that do not provide immediate or same-day screening test results (e.g. molecular or conventional cytological methods) may not receive their screening test results.
Data source	Main source: patient records at HIV clinic If data are not available from patient records at the HIV clinic, they might be obtained from: • Health information systems • Dedicated projects
Frequency	At program level: according to local needs, e.g. annually, quarterly, monthly; at IeDEA level: annually
Disaggregation	• by age group or range • by screening visit type • by screening method You can find more information about disaggregation below (paragraph: indicator disaggregation).
Data guidelines	This indicator monitors the linkage between the screening facility and the laboratory, and therefore is most applicable to screening methods that do not allow for immediate or same-day return of screening test results, such as some molecular or conventional cytological methods. It can be used to identify the need for active follow-up with screened women who do not know their screening test results. Women should receive their screening test results as soon as possible within 6 months in order to start appropriate treatment when needed; therefore, screening test results need to be communicated within 6 months after screening.
Additional comments	We acknowledge that other elements may be important to include for better understanding and interpreting of this indicator. For example, some screening tests can be obtained at point of care, or sent to the laboratory; screening test results can be received in person, by phone, by mail or other. However, due complexity to collect and implement this data, we did not include this type of information in this indicator.

Title	**RESCREENED AFTER A PREVIOUS NEGATIVE RESULT, WITHIN RECOMMENDED SCREENING INTERVAL**
Definition	"Women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" who were rescreened (after a previous negative result) within the recommended screening interval Recommended screening interval for women living with HIV* • if previously screened negative with HPV DNA: every 3 to 5 years • if previously screened negative with VIA or cytology: every 3 years
Numerator	Number of "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" who received a previous negative screening test, and have been rescreened within the recommended screening interval
Denominator	Total number of "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" received a previous negative screening test
Calculation	numerator/denominator per screening interval
Purpose and rationale	Purpose: this indicator measures whether women living with HIV who should return for a routine rescreening within the recommended screening interval. Rationale: the WHO suggests a regular screening interval of every 3 to 5 years for women living with HIV who were screened negative with an HPV DNA as the primary screening test. If VIA or cytology are used as the primary screening, WHO suggests a regular screening interval of every 3 years. Rescreening visit within the recommended screening interval is a critical part of comprehensive routine preventive care for cervical cancer.
Data source	Main source: patient records at HIV clinic If data are not available from patient records at the HIV clinic, they might be obtained from: • Health information systems • Dedicated projects
Frequency	At program level: according to local needs; e.g. annually; at IeDEA level: annually
Disaggregation	• by age group or range You can find more information about disaggregation below (paragraph: indicator disaggregation).
Data guidelines	This indicator includes only women who were screened and had a negative screening test result. We acknowledge that recommended screening period depends on which screening method is used (HPV DNA; VIA or cytology). In the interest of simplicity, we recommend to calculate this indicator for a 3-years period.
Additional comments	This indicator applies to women who were previously screened and received a screening test negative result. In the interest of simplicity, we do not record women, who are not eligible for screening for medical reasons, such as women who had a hysterectomy with no residual cervix, or women who refused screening, or other reasons. We acknowledge that other elements may be important to include for better understanding and interpreting this indicator. E.g., invitation to follow up can be patient initiated, recalled by HIV clinic or by cervical cancer screening clinic. However, due complexity to collect and implement this data, we did not include this type of information in this indicator.

Secondary prevention - triage

Title	RECEIVED TRIAGE EXAMINATION RATE
Definition	Screen-positive “women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest” who received a triage examination in a 12-month period Screen-positive women are women who were screened positive with the primary screening test.
Numerator	Number of screen-positive “women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest” who received a triage examination in a 12-month period
Denominator	Total number of screen-positive “women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest” in a 12-month period
Calculation	numerator/denominator per 12-month period
Purpose and rationale	Purpose: to measure whether all those who needed a triage examination received a triage examination. Rationale: WHO recommends using HPV DNA detection as the primary cervical screening test for women living with HIV that is followed by a triage test for those who tested positive rather than VIA.
Data source	Main source: patient records at HIV clinic If data are not available from patient records at the HIV clinic, they might be obtained from: • Health information systems • Dedicated projects • Service delivery data (triage or screening facility)
Frequency	at program level: according to local needs, e.g. annually, quarterly, monthly; at IeDEA level: annually
Disaggregation	• by age group or range • by triage method • by screening visit type You can find more information about disaggregation below (paragraph: indicator disaggregation).
Data guidelines	This indicator is applicable to screening strategies that include a triage step between the primary screening test and precancerous lesion treatment or further evaluation and diagnosis. This indicator should be calculated for a 12-month period. However, if other time periods are required by local program needs, the definition of the given time period can be adjusted.
Additional comments	Triage testing is performed in women who had a positive primary screening result. In a screen, triage and treat approach using HPV DNA detection as the primary screening test among women living with HIV, WHO recommends partial genotyping, colposcopy, VIA or cytology to triage women with a positive HPV DNA test.

Title	TRIAGE EXAMINATION POSITIVITY RATE
Definition	Screen-positive "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" with a positive triage examination result in in a 12-month period
Numerator	Number of "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" who received a positive triage examination result in a 12-month period
Denominator	Total number of screen-positive "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" who received a triage examination in a 12-month period Screen-positive women are women who were screened positive at the primary screening test.
Calculation	numerator/denominator per 12-month period
Purpose and rationale	Purpose: to measure the positivity rate of the triage test. Rationale: WHO recommends to use HPV DNA detection as the primary cervical screening test for women living with HIV that is followed by a triage test for those who tested positive.
Data source	Main source: patient records at HIV clinic If data are not available from patient records at the HIV clinic, they might be obtained from: • Health information systems • Dedicated projects • Service delivery data (triage or screening facility)
Frequency	At program level: according to local needs, e.g. annually, quarterly, monthly; at IeDEA level: annually
Disaggregation	• by age group or range • by triage method • by screening visit type You can find more information about disaggregation below (paragraph: indicator disaggregation).
Data guidelines	This indicator is applicable to screening strategies that include a triage (or secondary screening) step between the primary screening test and precancerous lesion treatment or further evaluation and diagnosis. This indicator should be calculated for a 12-month period. However, if other time periods are required by local program needs, the definition of the given time period can be adjusted.
Additional comments	Triage test is performed in women who had a positive primary screening result.

Title	TRIAGE EXAMINATION PROVISION RATE
Definition	Screen-positive “women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest” who attended the triage visit and received a triage examination in a 12-month period Screen-positive women are women who were screened positive with the primary screening test.
Numerator	Number of screen-positive “women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest” who attended the triage visit and received a triage examination in a 12-month period
Denominator	Number of screen-positive “women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest” who attended the triage examination visit in a 12-month period
Calculation	numerator/denominator per 12-month period
Purpose and rationale	Purpose: to monitor service provision and referral process by measuring completion of a triage examination for women attending a triage visit Rationale: provision of triage examination can be disturbed due many reasons (e.g. stockouts, women presenting with cervicitis or other infection preventing examination completion, etc.)
Data source	Main source: patient records at HIV clinic If data are not available from patient records at the HIV clinic, they might be obtained from: • Health information systems • Dedicated projects • Service delivery data (triage or screening facility)
Frequency	At program level: according to local needs, e.g. annually, quarterly; at IeDEA level: annually
Disaggregation	• by age group or range • by triage method • by screening visit type You can find more information about disaggregation below (paragraph: indicator disaggregation).
Data guidelines	This indicator is applicable to screening strategies that include a triage step between the primary screening test and precancerous lesion treatment or further evaluation and diagnosis. This indicator should be calculated for a 12-month period. However, if other time periods are required by local program needs, the definition of the given time period can be adjusted.
Additional comments	Good data system functionality is required to inform this indicator.

Secondary prevention – preventative treatment

Title	PRECANCEROUS LESIONS POST-TREATMENT FOLLOW-UP FOR RATE
Definition	"Women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" treated for precancerous lesions who return for a post-treatment follow-up screening test in a 12-month period
Numerator	Number of "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" treated in the previous year for precancerous lesions who returned for a post-treatment follow-up screening test in a 12-month period
Denominator	Total number of "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" treated in the previous year for precancerous lesions a 12-month period
Calculation	numerator/denominator per 12-month period
Purpose and rationale	Purpose: to determine the success of a previous treatment for precancerous lesions. Rationale: with successful treatment for precancerous lesions, likelihood to develop cervical cancer is significantly reduced. WHO recommends post-treatment follow up at 1 year from previous treatment.
Data source	Main source: patient records at HIV clinic If data are not available from patient records at the HIV clinic, they might be obtained from: • Health information systems • Dedicated projects • Service delivery data (triage or screening facility)
Frequency	At program level: according to local needs, e.g. annually; at IeDEA level: annually
Disaggregation	• by age group or range • by treatment type for precancerous lesions You can find more information about disaggregation below (paragraph: indicator disaggregation).
Data guidelines	This indicator should be calculated for a 12-month period. However, if other time periods are required by local program needs, the definition of the given time period can be adjusted.
Additional comments	Post-treatment follow-up screening – a visit which uses a screening test to determine the success of a previous treatment for precancerous lesions.

Tertiary prevention

Title	SUSPECTED CERVICAL CANCER CASES RATE
Definition	Screened “women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest” with suspected cervical cancer in a 12-month period
Numerator	Number of screened “women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest” with suspected cervical cancer in a 12-month period
Denominator	Total number of screened “women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest” in a 12-month period
Calculation	numerator/denominator per 12-month period
Purpose and rationale	Purpose: this indicator is important to understand the demand for screening and treatment services and planning the program’s resources. Rationale: cervical cancer can be prevented and treated with more success if detected earlier.
Data source	Main source: patient records at HIV clinic If data are not available from patient records at the HIV clinic, they might be obtained from: • Health information systems • Dedicated projects • Service delivery data
Frequency	At program level: according to local needs, e.g. annually, quarterly, monthly; at IeDEA level: annually
Disaggregation	• by age group or range • by screening visit type • by screening method You can find more information about disaggregation below (paragraph: indicator disaggregation).
Data guidelines	Data collection for this indicator should be implemented based on the screening strategy used. If screen and treat strategy is used, suspected cancer diagnosis may be identified at the primary screening test, for example VIA when used as primary screening test. But for screen-triage-treat strategies, suspected cases can be identified at the triage step, for example at VIA when used as triage test following HPV positive testing.
Additional comments	In some screening strategies, suspected cases may be referred for further examination and treatment decision. This indicator should be calculated for a 12-month period. However, if other time periods are required by local program needs, the definition of the given time period can be adjusted.

Title	CONFIRMED CERVICAL CANCERS RATE
Definition	Screen-positive “women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest” diagnosed with invasive cervical cancer in a 12-month period Screen-positive refers to all women testing positive on a primary screening test. Cervical cancer should be diagnosed histopathologically.
Numerator	Number of screen-positive “women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest” diagnosed with invasive cervical cancer in a 12-month period
Denominator	Total number of screen-positive “women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest” in a 12-month period
Calculation	numerator/denominator per 12-month period
Purpose and rationale	Purpose: to monitor the number of confirmed cervical cancer cases. Rationale: Monitoring how many of screened positive women are diagnosed with cervical cancer can be used to better organize prevention and treatment services.
Data source	Main source: patient records at HIV clinic If data are not available from patient records at the HIV clinic, they might be obtained from: • Health information systems • Dedicated projects • Service delivery data
Frequency	At program level: according to local needs, e.g. annually; at IeDEA level: annually
Disaggregation	• by age group or range • by screening visit type • by screening method You can find more information about disaggregation below (paragraph: indicator disaggregation).
Data guidelines	This indicator refers to women who tested positive at the primary screening test regardless which screening strategy is used (screen and treat, or screen-triage-treat). This indicator should be calculated for a 12-month period. However, if other time periods are required by local program needs, the definition of the given time period can be adjusted.
Additional comments	Disaggregation by screening visit type is strongly recommended, due to importance for both patient and program to monitor and compare rates of cancer in first time screenings, rescreening and post-treatment follow-up.

Impact and Linkage

Title	AGE-SPECIFIC CERVICAL CANCER INCIDENCE RATE
Definition	New invasive cervical cancer cases diagnosed in "women living with HIV/AIDS enrolled in care with at least one HIV clinic visit during the period of interest" in a specific age group or range in a 12-month period For this indicator incident cervical cancer is defined as squamous cell carcinoma, adenocarcinoma or unspecified invasive cervical cancer newly diagnosed six months or more after screening for pre-cancer. This definition therefore excludes screening-detected cancers. Cancers should be diagnosed histopathologically.
Numerator	Number of new invasive cervical cancer cases diagnosed in "women living with HIV/AIDS enrolled in care with at least one HIV clinic visit during the period of interest" in a specific age group or range in a 12-month period
Denominator	Total number of "women living with HIV/AIDS enrolled in care with at least one HIV clinic visit during the period of interest" in a specific age group or range in a 12-month period
Calculation	numerator/denominator multiply by 100 000 per 12-month period
Purpose and rationale	Purpose: age-specific cervical cancer incidence measures program impact on morbidity. Rationale: the intended impact of a screening program is to reduce morbidity from cervical cancer.
Data source	Main source: patient records at HIV clinic If data are not available from patient records at the HIV clinic, they might be obtained from: • Health information systems • Dedicated projects Cancer cases can be identified in routine care, through active follow-up and/or linkage to the screening registries and/or population-based cancer registries.
Frequency	At program level: according to local needs, e.g. annually; at IeDEA level: annually
Disaggregation	• by age group or range You can find more information about disaggregation below (paragraph: indicator disaggregation).
Data guidelines	The incidence rate is usually reported as number of incident cases per 100 000 person-years of observation. If data quality allows, women lost to follow-up, transferred out or dead will be censored in the analysis. This indicator should always include a specific age-range or group. This indicator should be calculated for a 12-month period. However, if other time periods are required by local program needs, the definition of the given time period can be adjusted.
Additional comments	Interpreting the result of this indicator can be influences by the time of the program implemented. At the beginning of the screening program, cervical cancer incidence may increase due higher number of women screened than before. However, later there may be a gradual reduction in new cases of invasive diseases detected, but increase in pre-cancers detection. To evaluate and detect the real impact of screening to cervical cancer incidence, it may take a decade.

Title	HIV TESTING AND COUNSELING SERVICE PROVISION RATE
Definition	Women with previously unknown HIV status who received testing and counseling service for HIV at their cervical screening visit, and now know their HIV status in a 12-month period
Numerator	Number of women with previously unknown HIV status who received a positive or negative HIV test result at their cervical screening visit in a 12-month period
Denominator	Total number of women with unknown HIV status attending cervical screening in a 12-month period
Calculation	numerator/denominator per 12-month period
Purpose and rationale	Purpose: to monitor the success of HIV service integration in cervical cancer screening services. Rationale: Some women who attend cervical screening and unaware of their HIV status. HIV is a risk factor for developing cervical cancer, and therefore it is important to provide testing to all women who are visiting screening.
Data source	Main source: patient records at HIV clinic If data are not available from patient records at the HIV clinic, they might be obtained from: • Health information systems • Dedicated projects • Service delivery data
Frequency	At program level: according to local needs; at IeDEA level: annually
Disaggregation	• by age group or range You can find more information about disaggregation below (paragraph: indicator disaggregation).
Data guidelines	Unknown HIV status typically includes women who have never been tested and those who received a negative result more than 3 months ago. This indicator should be calculated for a 12-month period. However, if other time periods are required by local program needs, the definition of the given time period can be adjusted.
Additional comments	This indicator is applicable for sites that offer HIV testing and counseling services during cervical screening.

Recommendations in indicators' tables are based on following literature:

1. World Health Organization. WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention. World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.
2. World Health Organization, et al. *Global strategy to accelerate the elimination of cervical cancer as a public health problem*. World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO
3. World Health Organization. *WHO framework for strengthening and scaling-up of services for the management of invasive cervical cancer*. World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.
4. World Health Organization. *Improving data for decision-making: a toolkit for cervical cancer prevention and control programmes*. World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.

Terminology

Cervical cancer - A malignant tumor of the cervix, the lowermost part of the uterus.

Cervical cancer screening sample – A cervical sample can be taken as a conventional smear or as fluid-based cytology

Chemotherapy for cervical cancer (adjusted) – it usually involves using either a single chemotherapy drug or a combination of different chemotherapy drugs to kill the cancerous cells.

Cold knife conization – The removal of a cone-shaped area from the cervix, including portions of the outer (ectocervix) and inner cervix (endocervix), usually carried out in a hospital; the amount of tissue removed will depend on the size of the lesion and the likelihood of finding invasive cancer.

Compliance – The act of following a medical regimen or schedule correctly and consistently

Cryotherapy – By applying a highly cooled metal disc (cryoprobe) to the cervix and freezing the abnormal areas (along with normal areas) covered by it, cryotherapy eliminates precancerous areas on the cervix by freezing (i.e. it is an ablative method).

HPV – An infection that causes warts in various parts of the body, depending on the strain. The International Agency for Research on Cancer currently defines 12 high-risk HPV types which are associated with cancers in humans (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) and additional types for which there is limited evidence of carcinogenicity (types 68 and 73).

Invasive cancer – Cancerous tumors that have broken out of the lobule where they began growing and have the potential to invade other parts of the body

Loop Electrosurgical Excision Procedure (LEEP) – The removal of abnormal areas from the cervix and the entire transformation zone, using a loop made of thin wire powered by an electrosurgical unit; the loop tool cuts and coagulates at the same time; this is followed by use of a ball electrode to complete the coagulation.

Negative test result – A test result that shows the substance or condition the test is supposed to find is not present at all or is present, but in normal amounts.

Palliative care – A multidisciplinary approach to specialized medical care for people with serious illnesses, focusing on providing patients with relief from symptoms, pain, physical stress, and mental stress to improve quality of life for both the patient and the patient's family.

Positive screening result – A test result that shows that a person has the disease, condition, or biomarker for which the test is being done.

Positive triage examination result – A test result that shows that a person has the disease, condition, or biomarker for which the test is being done (adjusted).

Normal/negative = no indication of precancerous lesions

Abnormal/positive = precancerous lesions suspected or confirmed

Post-treatment complication (adjusted) – a medical problem that occurs after a treatment. The complication may be caused by the disease, procedure, or treatment or may be unrelated to them.

Post-treatment follow-up screening – A visit which uses a screening test to determine the success of a previous treatment for precancerous lesions.

Precancerous lesion – Non-invasive lesion with a predictable likelihood of becoming malignant.

Radiation therapy – it uses high energy x-rays to kill cancer cells. Depending on the stage of the cervical cancer, radiation therapy may be used: As a part of the main treatment. For some stages of cervical cancer, the preferred treatment is radiation alone or surgery followed by radiation.

Radical hysterectomy – Surgical removal of the entire uterus, cervix, tissue on the side of the uterus including the fallopian tubes and ligaments; nodes and ovaries may also be removed.

Rescreening – A screening visit attended by a woman after a previous negative result on a screening test. This visit is part of routine preventive care and should be conducted within the recommend interval for screening

Screening – A public health intervention provided to an asymptomatic target population; it is not undertaken to diagnose a disease, but to identify individuals with increased probability of having either the disease itself or a precursor of the disease.

Simple hysterectomy – Surgery to remove only the uterus and the cervix alone.

Suspected cancer – any cervical lesion that is suspicious for cancer.by health-care provider **Referral** – the act of a doctor in which a patient is sent to another doctor for additional healthcare services.

Treatment of invasive cancer – Includes chemotherapy, radiation, and radical hysterectomy.

Treatment or precancerous lesions – Includes cryotherapy, LEEP, conization, and in some situations, simple hysterectomy.

Triage – Step or procedure typically performed between the screening and diagnosis or treatment procedures to further stratify individuals with positive primary screening results.

Indicator disaggregation

Indicators can be disaggregated by several different criteria. Most indicators can be disaggregated by the following criteria: age group or age range; screening visit types; screening (or triage) methods etc. For each indicator, we report recommended criteria for disaggregation in the indicator tables. Additional disaggregation allows breaking up aggregate indicator data into component parts providing more granular information. Additional disaggregation based on the level of facility and HIV status is not applicable in the presented indicators as they are intended to be used at IeDEA HIV facility levels to monitor women living with HIV through the cervical cancer control continuum.

To ensure high-quality and ideally internationally comparable data within the IeDEA consortium, indicators aim to collect and report data and data elements in a standardized and feasible way. Using additional disaggregation as recommended in this document can help to identify potential gaps in the continuum of cervical cancer prevention and care. However, using this feature increases the complexity of data collection and management. Both aggregated and disaggregated indicators have weaknesses and present only part of the information. Ideally, the most comprehensive approach integrates both aggregated and disaggregated indicators, by presenting aggregating data into one total and disaggregating that total into its components and additional elements. Therefore, additional disaggregation of indicators should be decided based on program context, priorities, and resources.

Age group or age range

- Inside of selected age range (25-49 years old) or outside of selected age range
- Younger than 25 years; 25-49 years old; 50-69 years old; and older than 70 years
- 5 years age groups

If none of these suggestions is available, please specify the age range or group that is used to inform indicators.

Note: We recommend these age ranges because WHO suggests starting regular cervical cancer screening at age of 25 years among women living with HIV, and to give priority to screening women living with HIV aged 25-49 years. When there are other recommendations for disaggregating an indicator by age group or age range available, it is noted in the indicator table.

An example (recommended baseline)

SCREENING TEST POSITIVITY RATE FOR THE PRIMARY SCREENING TEST
Numerator: Number of screened "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" who received a positive screening test result in a 12-month period
Denominator: Total number of screened "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" in a 12-month period

An example: additional disaggregation by inside or outside selected age range (25-49 years old)

SCREENING TEST POSITIVITY RATE FOR THE PRIMARY SCREENING TEST	
Numerator: Number of screened "women living with HIV/AIDS enrolled in care with at least one HIV clinic visit during the period of interest" who received a positive screening test result in a 12-month period	Inside of selected age range (25-49 years old)
	Outside of selected age range (younger than 25 or older than 49 years old)
Denominator: Total number of screened "women living with HIV/AIDS old enrolled in care with at least one HIV clinic visit during the period of interest" in a 12-month period	Inside of selected age range (25-49 years old)
	Outside of selected age range (younger than 25 or older than 49 years old)

An example: additional disaggregation by age groups

SCREENING TEST POSITIVITY RATE FOR THE PRIMARY SCREENING TEST	
Numerator: Number of screened "women living with HIV/AIDS enrolled in care with at least one HIV clinic visit during the period of interest" who received a positive screening test result in a 12-month period	Younger than 25 years
	25-49 years old
	50-69 years old
	Older than 70 years
Denominator: Total number of screened "women living with HIV/AIDS old enrolled in care with at least one HIV clinic visit during the period of interest" in a 12-month period	Younger than 25 years
	25-49 years old
	50-69 years old
	Older than 70 years

Screening visit type

- First time screenings and all other screenings
- First time screenings; routine rescreening (after last screening was negative) and post-treatment follow-up at 1 year (after last screening was positive)

An example (recommended baseline)

SCREENING TEST POSITIVITY RATE FOR THE PRIMARY SCREENING TEST	
Numerator: Number of screened "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" who received a positive screening test result in a 12-month period	First time screened women
	All other screened women
Denominator: Total number of screened "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" in a 12-month period	First time screened women
	All other screened women

An example: additional disaggregation by screening types

SCREENING TEST POSITIVITY RATE FOR THE PRIMARY SCREENING TEST	
Numerator: Number of screened "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" who received a positive screening test result in a 12-month period	First time screenings
	Routine rescreening (after last screening was negative)
	Post-treatment follow-up at 1 year (after last screening was positive)
Denominator: Total number of screened "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" in a 12-month period	First time screened women
	All other screened women
	Post-treatment follow-up at 1 year (after last screening was positive)

Some programs aggregate data on services delivered into simple overall totals for monitoring, without considering the screening history. This aggregate number is important to understand the demand for screening and treatment services and planning the program's resources. Some programs consider only data relevant to first time screenings, as a key to estimate whether a program is reaching screening naïve women, who are at high risk of having cervical pre-cancer. WHO recommends focusing on first time screenings in order to align with the goals of most programs, and because this information is key to reach global WHO targets. This indicator can therefore be disaggregated by first time, versus all screenings, or, if data quality allows, by first time screenings versus routine rescreening (after last screening was

negative) versus post-treatment follow-up at 1 year (after last screening was positive). Without an electronic registry, determining whether a screening is first time will depend on client self-reporting, which may introduce a misclassification bias.

Screening (or triage) methods

- Visual inspection methods
- Molecular methods
- Cytological methods

Visual inspection methods include visual inspection with acetic acid or with Lugol's iodine (VIA/VILI), done by naked eye or magnified by colposcope or camera and automated visual evaluation of digital images*.

Molecular methods include nucleic acid amplification tests (NAAT), as high-risk HPV DNA/NAAT or mRNA; DNA methylation* and protein biomarkers*, as HPV antibodies and oncoproteins.

Cytological methods include conventional Pap smear, Liquid-based cytology (LBC), and Dual staining to identify p16 and Ki-67.

*tests under evaluation – future tests.

Note: Additional disaggregation by this element depends on which method is available and used at the facility level.

An example (recommended baseline)

SCREENING TEST POSITIVITY RATE FOR THE PRIMARY SCREENING TEST	
Numerator: Number of screened "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" who received a positive screening test result in a 12-month period	All primary screening methods available and used
Denominator: Total number of screened "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" in a 12-month period	All screening methods available and used

An example: additional disaggregation by screening methods

SCREENING TEST POSITIVITY RATE FOR THE PRIMARY SCREENING TEST	
Numerator: Number of screened "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" who received a positive screening test result in a 12-month period	Visual inspection methods
	Molecular methods
	Conventional cytological methods
Denominator: Total number of screened "women living with HIV/AIDS 25-49 years old enrolled in care with at least one HIV clinic visit during the period of interest" in a 12-month period	Visual inspection methods
	Molecular methods
	Conventional cytological methods

Note: Indicators that require recording screening (primary or triage) results, we recommend using WHO standardized terminology for classifying the results of cervical screening tests:

VIA results:

- Negative
- Positive (eligible for precancer treatment)
- Positive (suspected cancer)

Positive (eligible for pre-cancer treatment) and positive (suspected cancer) results are both considered as screen-positive (or triage-positive) for informing this indicator. If the VIA result is inconclusive or indeterminate, the screening procedure should be repeated or a colleague should be consulted. When these options are not available, the screening test result should be rated as positive for the indicator calculations.

Pap smear / cytology:

- Normal (negative for intraepithelial lesions or malignancy)
- Abnormal (any epithelial cell abnormality)

Any epithelial cell abnormality is considered a positive result. Women with an abnormal result on a Pap smear screening test are therefore considered screen-positive.

HPV test results:

- Negative
- Positive
- Retest required

Other elements

Some indicators can be disaggregated in addition by indicator-specific elements:

- **High-risk HPV subtypes**: if there is additional data on specific HPV high-risk sub-types, this can be disaggregated in addition.
- **Treatment types for precancerous lesions**: cryotherapy (single-visit approach, previously postponed, and referred-in); LEEP; conization or simple hysterectomy
- **Treatment types for cervical cancer**: surgery; chemotherapy; radiotherapy; combination; or not applicable
- **Complication of treatment**: bleeding (more than menstrual flow), abdominal pain, foul-smelling discharge or fever
- **Duration of complication of treatment**: short term or long-term complications
- **Geography or Location**: province, region, district, or other appropriate administrative boundaries; predominately urban or rural, mixed urban/rural; regional, national or international level etc.

Note: In this report, we have mainly considered elements for disaggregation that are relevant to women regardless the HIV status. Within IeDEA collaboration, working mainly with women living with HIV, the following additional patient and treatment elements can be considered:

- **Antiretroviral therapy (ART)** is the recommended treatment for HIV; it involves using a combination of antiretroviral drugs every day to control the HIV virus. The type of drugs that are prescribed, the time when treatment started, if treatment was paused etc. are important factors that may influence the health outcome of women living with HIV.
- **HIV viral load** is the amount of HIV in the blood of someone who has HIV. It has the highest value during the acute phase of HIV, and without or failing HIV treatment.
- **CD4 cell count** informs us about the HIV treatment progress and control of HIV. A normal CD4 cell count is between 500 to 1400 cells per cubic millimeter of blood. CD4 cell count decreases in people living with HIV who are not receiving effective treatment.

Combining elements for disaggregation

The number of elements used to disaggregate this indicator in addition is optional and depends on data availability and quality. In cases where more than one element is used, both numerator and denominator must be disaggregated appropriately. For example, when both age disaggregation and screening visit type is used to disaggregate indicator in addition, each age category (inside or outside of selected age range (25-49 years old)) should be disaggregated in addition by categories of screening visit types (e.g. first time screenings and all other screenings), as presented in the table below.

An example: combining elements for disaggregation

SCREENING TEST POSITIVITY RATE FOR THE PRIMARY SCREENING TEST		
Numerator: Number of screened "women living with HIV/AIDS enrolled in care with at least one HIV clinic visit during the period of interest" who received a positive screening test result in a 12-month period	25-49 years old	First time screened women
		All other screened women
	Outside of selected age range (<25 and >49 years old)	First time screened women
		All other screened women
Denominator: Total number of screened "women living with HIV/AIDS enrolled in care with at least one HIV clinic visit during the period of interest" in a 12-month period	25-49 years old	First time screened women
		All other screened women
	Outside of selected age range (<25 and >49 years old)	First time screened women
		All other screened women

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IeDEA Central Africa

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IeDEA East Africa

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IeDEA West Africa

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11.2. Supplementary Information Publication 2

Asangbeh-Kerman SL, **Davidović M**, Taghavi K, et al. Cervical cancer prevention in countries with the highest HIV prevalence: a review of policies. BMC Public Health. 2022 Aug 10;22(1):1530.

The supplementary information is available from: https://doi.org/10.1186/s12889-022-13827-0, accessed February 13, 2024.

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Table S1. Other Primary prevention strategies

Country	Sex education*	Condom Use	Voluntary Male Medical Circumcision	Warnings about tobacco use
Botswana	Yes	Yes	Yes	Yes
Eswatini[£]	Yes	Yes	No	Yes
Lesotho[£]	Yes	Yes	No	Yes
Malawi[£]	Yes	Yes	Yes	Yes
Mozambique	Yes	Yes	No	Yes
Namibia	Yes	Yes	Yes	Yes
South Africa	Yes	Yes	Yes	Yes
Zambia	Yes	Yes	No	Yes
Zimbabwe	Yes	Yes	No	Yes

Yes – recommended or present; *development of IEC material

Table S2. Treatment of invasive cervical cancer and palliative care

Country	Treatment of invasive cancer	Palliative care
Botswana	Radiotherapy	Available
Eswatini	Not reported	Available
Lesotho	Not available (Treatment of invasive cancer done in South Africa)	Available, centralized
Malawi	Surgery, chemotherapy	Available, centralized
Mozambique	Not reported	NR
Namibia	Surgery, chemotherapy, radiotherapy	NR
South Africa	Surgery, chemotherapy, radiotherapy	Available
Zambia	Chemotherapy, radiotherapy	Available
Zimbabwe	Radiotherapy (Treatment for invasive cancer is mostly done in private health facilities at high cost)	Available, centralized

Table S3. Cost of services for clients

Country	HPV vaccination	Cervical screening	Diagnostic procedures	Treatment of cervical pre-cancer	Treatment of invasive cancer
Botswana	NR	Free for vulnerable groups	Free for vulnerable groups	Free for vulnerable groups	NR
Eswatini*	NR	NR	NR	NR	NR
Lesotho	Free in government facilities	Free	NR	NR	NR
Malawi	Free	Free	NR	Free	NR
Mozambique	NR	NR	NR	NR	NR
Namibia*	NR	NR	NR	NR	NR
South Africa	Free in school and about $65 out of school	Free	Free in public facilities	Free	Free in public facilities
Zambia	NR	NR	NR	NR	NR
Zimbabwe	NR	Free	Unaffordable [±]	Treatment is charged in some institutions (particularly LEEP)	Prohibitive [±]

*Financial and technical resources are not available to ensure services are available and affordable to women (experts' report); [±]As reported by country expert; NR = not reported

Table S4. Other responses from country experts

	Item/service									
Country	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Botswana	Yes	Yes	Yes	Yes	Partially available	Yes	Unable to comment	Unable to comment	Needs strengthening	Needs strengthening
Eswatini*	Yes	Yes	Yes	No	No	No	No	No	No	No
Lesotho	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No
Malawi	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mozambique	Yes	No	No	Yes	Yes	Yes	No	Yes	No	No
Namibia*	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	No
South Africa	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zambia	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Zimbabwe	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

1. Single visit approach recommended
2. Clinical practice guidelines for CC screening specific to HIV infected women
3. Guidelines for HIV infected women separate document from clinical practice guidelines
4. Functional multidisciplinary platform to foster partnership and collaboration and set the national agenda
5. National guidelines for health workers for all components of comprehensive cervical cancer prevention and control
6. Financial and technical resources to implement the policy and plan and ensure that services are available and affordable to girls and women
7. Communication strategies to educated the community and advocate for support of national policies
8. A training plan in place as well as supervisory mechanisms for quality control and assurance of the programme
9. A functional referral system that links screening services with the treatment of precancerous lesions and invasive cancer
10. Functioning monitoring systems to track coverage of HPV vaccination, screening and follow-up treatment

Table S5. Data extraction sheet

General information	Country
	Title of policy document
	Source (e.g. location)
	Period of validity
Human papillomavirus vaccination	Recommended vaccine
	Target population and age
	Vaccination strategy
	Cost for clients
	Integrated in national programme on immunization (Yes/No)
	Indicators for monitoring vaccination programme
	Targets
Screening and treatment of cervical precancerous lesions and invasive cancer	Organised or Opportunistic
	Target age group
	Specifications for WLHIV?
	Entry point for screening (family planning, HIV clinic, STI clinic)
	Screening method (s)
	Cost of screening for clients
	Diagnostic capacity (present/absent/rare)
	Cost of diagnosis for clients
	Treatment for precancerous lesions (cryo, cold coagulation, surgery)
	Cost of treatment of pre-cancer for clients
	Treatment for invasive cervical cancer (radio, chemo, surgery, not available)
	Cost of treatment of invasive cervical cancer for clients
Follow-up	Follow-up intervals for screen-positive and screen-negative women defined (Yes/No).
	Palliative care (available/not available)
	Cancer registry (present/absent)
	Indicators for monitoring screening, treatment and follow-up
	Targets for screening, treatment and follow-up
Availability of data systems	Data entry (electronic/paper-based)
Indicators and targets	Indicators and targets for CC prevention will be extracted

Table S6. Extract from WHO's CC prevention and control toolkit for cervical cancer prevention and control programs

Question	Response options
Is there a national health policy, plan or strategy? Does it include cervical cancer prevention and control?	HPV Vaccination
	Screening PCL treatment
	Invasive Cervical Cancer
	Does not address cervical cancer prevention and control
Is there a national policy, plan or strategy for cancer prevention and control? Does it include cervical cancer prevention and control?	HPV Vaccination
	Screening PCL treatment
	Invasive Cervical Cancer
	Does not address cervical cancer prevention and control
Is there a policy, plan or strategy specific to cervical cancer (in addition to the national cancer prevention and control policy)? What does it cover?	HPV Vaccination
	Screening PCL treatment
	Invasive Cervical Cancer
	Does not address cervical cancer prevention and control
If policies, plans or strategies which address cervical cancer prevention and control exist, what cervical cancer screening method do they recommend?	Cytology/Pap smear
	VIA
	VILI
	HPV DNA test Other (specify):
	No recommendation
What method for the treatment of precancerous lesions is recommended by policies, plans or strategies which address cervical cancer?	Cryotherapy
	LEEP
	Conization
	Thermal/cold coagulation
	Other (specify):
	No recommendation
Is a Single Visit Approach for cervical cancer screening and precancerous lesion treatment recommended by policies, plans or strategies?	□ Yes □ No
Are there standardized national clinical practice guidelines for the following cervical cancer services?	Screening
	□ Yes □ No
	Treatment of precancerous lesions Management of invasive cervical cancer
	□ Yes □ No

	□ Clinical practice guidelines do not exist for cervical cancer services
Are there clinical practice guidelines for cervical cancer screening specific to HIV infected women?	□ Yes □ No
If Yes, are these guidelines a separate document from the clinical practice guidelines for screening noted above?	□ Yes □ No

Table S7. WHO checklist for a comprehensive cervical cancer prevention and control programme

N	Item
1	Functional multidisciplinary platform to foster partnership and collaboration and set the national agenda
2	Comprehensive national policy or plan on cervical cancer prevention and control
3	National guidelines for health workers for all components of comprehensive cervical cancer prevention and control
4	Financial and technical resources to implement the policy and plan and ensure that services are available and affordable to girls and women
5	Communication strategies to educated the community and advocate for support of national policies
6	A training plan in place as well as supervisory mechanisms for quality control and assurance of the programme
7	HPV vaccination as a population based strategy to an appropriate cohort in the target age group of 9 and 13 year old girls
8	Cervical cancer programme to screen and treat every woman between 30 and 49 years old at least once in their lifetime
9	A functional referral system that links screening services with the treatment of precancerous lesions and invasive cancer
10	Functioning monitoring systems to track coverage of HPV vaccination, screening and follow-up treatment
11	Existence of a cancer registry as part of the health information system to monitor cervical cancer incidence and mortality

Table S8. List of indicators and targets extracted from included policy documents

Country / Plan title	Indicators	Targets
Malawi		
National Cervical Cancer Control Strategy	HPV vaccine coverage rate: Percentage of girls aged 9-13years who have received all the doses of the HPV vaccine in the previous 12-month period	90%
	Screening coverage rate: Percentage of women 25-49 years who have been screened with VIA for the first time with in the previous 12-month period	80%
	Treatment rate for VIA positive women: percentage of VIA- positive women receiving treatment in the previous 12-month period	90%
	Treatment of cancers: percentage of curable cervical cancer patients receiving adequate care	10% by 2020
	Percentage of women receiving palliative care for advanced cervical cancer	50% by 2020
	Decreased incidence from invasive cervical cancer	
	Decreased mortality from invasive cervical cancer	
Standard Operating Procedures for CC Services	Number of clients screened for cervical cancer disaggregated by age	
	Number of clients screened for cervical cancer disaggregated by HIV status	
	Number of clients screened disaggregated by reason for facility visit	
	Number of clients screened disaggregated by screening method	
	Cervical cancer screening results	
	Number of cancer suspects disaggregated by age	
	Total number of clients treated	
	Number of clients treated disaggregated by treatment option	
	Number of clients referred disaggregated by referral reasons	
	Number of clients that received feedback	
	Percentage of facilities providing cancer screening service	

	Number of cervical cancer service providers trained	
	Number of active service providers during the past three months	
National Cancer Prevention and Control Strategy	Percentage of facilities providing cancer screening, early detection and linkages to care	Increase by 60% the number of facilities providing early detection and treatment services
	Percentage of level 3-5 facilities offering basic cancer diagnosis, treatment and palliative care	Expand to 80% the number of level 3-5 facilities offering basic cancer diagnosis, treatment and palliative care by 2022
	Number of facilities with systems in place to meet the requirements for cancer surveillance, research, and strategic information systems	To strengthen cancer surveillance, research and strategic information systems
	Number of facilities that are well-equipped with the proper infrastructure, specialists, and technologies for cancer prevention and control	Number of facilities that are well-equipped with the proper infrastructure, specialists, and technologies for cancer prevention and control
	Number of improved policies or partnerships established for prevention, treatment, care and rehabilitation of cancer	To establish a high level mechanisms for multi-sectoral coordination and partnership for prevention, treatment, care and rehabilitation of cancer
	CC incidence	
	CC mortality	
NCDs Annual Programme Report	Proportion of CC deaths related to inpatient admissions	
National Cervical Cancer Strategic plan	Cervical cancer age-standardised incidence rate	60/100000 by 2026 (same target for all indicators listed in this plan)
	Cervical cancer Age Standardized mortality rate	40/100000
	Cervical cancer included on government funding budget line items for MOH	

	Number of facilities providing cervical cancer control services	150
	Number of CSOs actively engaged in advocacy in cervical cancer control activities	40
	Established and operational social grants for cancer patients to access treatment	
	A costed implementation plan for the cervical cancer control strategy	1
	Number of strategic plan dissemination meetings conducted (including launch of the strategic plan)	
	Number of people trained per category e.g. CSOs affiliates, peers, youth etc.	700
	Published IEC materials	
	Number of community representatives engaged in cervical cancer public awareness activities (including traditional leaders, church leaders etc)	60
	Number of active cervical cancer champion programs in the country	40
	Number of cervical cancer patients enrolled in the champion programs	400
	Number of public cervical cancer awareness events conducted	25
	Number of role models participating in cervical cancer prevention activities	25
	Number of males attending public cervical cancer awareness events	3000
	Topics on cervical cancer prevention included in the curricula for primary and secondary schools	
	Number of orientation meeting conducted	4
	Number of people oriented in effective messaging of cervical cancer prevention and control	300
	Percentage of eligible adolescent girls who received the HPV vaccine	95
	Percentage of health facilities offering HPV vaccine	90
	Percentage of health facilities without stock out of HPV vaccine among those offering HPV vaccine	90
	Number of adolescents vaccinated through outreach clinics, village clinics or mobile clinics	200000
	Number of health facilities offering HPV vaccine in out of facility settings	950
	Number of public cervical cancer awareness events conducted	12

	Percentage of women undergoing period cervical cancer screening among those exposed women to occupational hazards	50
	Number of providers trained in providing cervical cancer services by cadres	2000
	Number of providers trained in colposcopy and LEEP per cadre	70
	Number of health professional training institutions providing training modules in cervical cancer screening and preventive therapy	12
	Percentage increase in number of cervical cancer screening and treatment sites	80
	Increase treatment rate for precancerous lesions	85
	Increase screening coverage	72
	Percentage of HIV/ART clinics providing cervical cancer screening and treatment services	90
	Percentage of cervical cancer screening and treatment sites without stock out of commodities used in screening and treatment services	90
	Number of mentorship and supportive supervisions conducted per year	4
	Number of screening/treatment clinics using visual devices for quality assurance	60
	Percentage of cervical cancer screening and treatment sites whose submitted routine services data has less than 5% of inconsistencies	95
	Percentage of referred women who provided feedback after receiving care	90
	Percentage of facilities providing HPV based cervical	50
	Percentage of women who are linked to care upon testing HPV positive	70
	Percentage of women who receive diagnostic services among those referred for cervical cancer diagnosis	90
	Percentage of women who receive cervical cancer treatment services among those diagnosed with cervical cancer	90
	Percentage of health facilities with operational infrastructure for cervical biopsy sample collection, tissue processing and preparation for histopathologic examination among facilities providing cervical cancer control services	90

	Number of lab scientists/technicians trained in tissue processing and preparation for histopathologic examination	60
	Number of hospitals offering competence-based gynaecologic oncology surgical training	4
	Number of gynaecologists with competence in gynaecologic surgical oncology from gynecologic oncology surgical trainings	15
	Number of central hospitals with designated accomodation facilities for cancer patients and their caregivers receiving outpatient cancer treatment	4
	Percentage of health facilities with tumor boards among those providing cancer treatment	90
	Average time (in weeks) taken from referral to cancer diagnosis	
	National cervical cancer care guidelines developed, disseminated and in use	
	Availability of functioning supportive care programs for cervical cancer patient	
	Percentage of cervical cancer patients receiving supportive care among all cervical cancer patients eligible for supportive care	90
	Percentage of facilities without stock out of cervical cancer treatment commodities among facilities providing cervical cancer treatment	90
	Number of training programs in cancer research	10
	Number of operational research studies conducted on cervical cancer	30
	Cervical cancer research included in the National Research Agenda	
	Number of research studies on cervical cancer disseminated through symposia or research dissemination conferences	15
	Cervical cancer facility reporting rate	100
	Number of staff trained in monitoring, evaluation and data management per cadre	1500
	Number of staff trained in cancer registration and surveillance	30
	Operational national monitoring and evaluation plan for cancer registries	
	Linkage system between the cancer registry database and the CECAP database developed, in use and maintained	

	Condom use at last sexual intercourse	
	Number of people reached with condom use education	
	Number of men circumcised	
Eswatini		
Sexual And Reproductive Health Annual Programme Report	Number of condoms distributed	
Zambia		
National Cancer Control Strategic Plan	Percentage of 9 – 13 year old girls completing full three-dose vaccination	Over 80% coverage of eligible girls
	Percentage of the eligible population accessing cervical cancer service	over 80% of women of reproductive age by 2021
	Percentage of eligible women screened at least once with VIA	80%
	Percentage of VIA positive women eligible for cryotherapy completing same-day treatment.	80%
	Number of sites offering LEEP services	from 25 to 132/132 sites
	Percentage of VIA positive women eligible for LEEP who complete LEEP treatment.	95% of eligible
	Number of sites offering VIA/Treatment	from 41 to 132/132 sites
	Percentage of women over the age of 25years receiving mHealth messages	above 80%
	Number eligible persons receiving cervical cancer treatment	over 80% of eligible patients
	Number of staff capable of performing VIA plus cryotherapy	train additional 300
Visual Inspection with Acetic Acid (VIA) and Cryotherapy: A Reference Manual for Trainers and Health Care Providers	Number of new women who received VIA screening in the target age range	85% by 5 years
	Percentage of new women screened with a VIA positive result positivity rate	Benchmark 5-10% a month
	Percentage of women referred for suspect cancer	Benchmark <1%/quarter
	Percentage of women referred for large lesions	Benchmark about 10%/month
	percentage of eligible cc screened new women screened and treated with cryotherapy on the same day	Benchmark 80% or above

	percentage of new VIA and cryotherapy eligible women who receive cryotherapy including SVA and those who postponed and returned) overall cryotherapy treatment rate	Benchmark 90% / month
	Number of new women referred to another site for advanced care and treatment : overall referral rate (suspect cancer and referrals for large lesions)	
	Percentage of all women who have confirmed cancer after referral	
	Percentage of new women who received treatment for large lesions after referral	
	Percentage of VIA positive women who postponed cryotherapy	
	Percentage of VIA + women who postponed cryotherapy and returned (for those who do not return, lost to treatment follow-up, will be deduced)	
	Percentage of women that receive treatment that return with post-treatment complication	
	Percentage of previously treated women (cryotherapy and LEEP) that return for 1-year follow-up visit.	
	Percentage of women who return for 1 year follow up visit after treatment in previous year and now have a VIA-negative result (cure rate)	
Lesotho		
National Multi-Sectoral Integrated Strategic Plan for the Prevention and Control of NCDs	HPV vaccination coverage sustained at >90%	
	Proportion of women screened for cervix cancer	
	Cancer treatment centre established in Lesotho by 2020	
	Number of girls (9-13 years old) vaccinated for HPV	
National Health Strategic Plan	Percentage of women provided cervical cancer screening	
	Number of women screened	
	Cervical cancer screening	
Clinical Practice Standards: CC Prevention. CC Prevention Practice Guidelines	Percentage of target population screened	
	Percentage of abnormal screening results test positivity	

	Percentage of facilities that are offering screening services	
	Percentage of health care providers trained in screening	
	Percentage of women with positive screening results test positivity	
	Treatment rate: percentage of women diagnosed with CIN2 treated	
	Incidence of CC	
	Mortality from CC	
Guidelines For Screening for Cervical Pre-Cancer in Lesotho	Percentage of women aged 25 and above screened	
	Coverage: Percentage of target population screened	
	Smear adequacy: Percentage of all smears that are identified by the laboratory as having endo-cervical cells.	
	Facility coverage: Percentage of health care facilities offering screening services.	
	Availability of skills: Percentage of health care providers trained in screening.	
	Turnaround time of screening method.	
	Diagnosis to treatment time.	
	Number of women screened.	
	Percentage of women with positive screening results.	
	Screening abnormality rates: VIA/VILI positive. Atypical squamous cells (ASC-US and ASC-H), AGUS, LSIL, HSIL, and HPV abnormality.	
	Treatment rate: Percentage of women diagnosed with HSIL treated	
	Incidence of invasive cervical cancer.	
	Mortality rate from cervical cancer.	
Zimbabwe		
National Cancer Prevention and Control Strategy for Zimbabwe	HPV vaccination coverage	85% by 2018
	Percentage of women 25-59 years old examined at least once for cancer of the cervix	25%
	Percentage of health facilities providing integrated HIV/STI/CC screening	60% by 2016

	Number of staff trained in integrated CC/breast/HIV/STI service per facility	100% provincial and district hospitals by 2016
		100% primary health care facilities by 2018
	Existence of functional radiotherapy services at Mpilo and Parirenyatwa hospital	100% functionality by 2018
	Availability of adequate human resources for cancer control	70% staffing level by 2018
	Availability of essential affordable cancer management medicines from NatPharm	
	Percentage of facilities HIV/STI and cancer integrated services	100% by 2018
	Percentage of clients accessing integrated HIV/STI and cancer services	100% by 2018
	Number of staff trained in integrated cancer/HIV/STI early detection and management services	100% by 2018
	Availability of a functional cancer database	2015
	Existence of a functional referral system at all systems	2015
	Incidence of CC	Down by 5%
	Mortality of CC	Down by 5%
The Zimbabwe Cervical Cancer Prevention and Control Strategy	HPV vaccination coverage for eligible girls (girls aged 11 years)	80%
	Percentage of districts offering vaccination	3%
	Screening coverage for women 30-49 years	from 13%-50% by 2020
	Increase in the percentage of women who have heard about CC	79%-90%
	Treatment rate for pre-cancer cryotherapy and LEEP	53%-80%
	Percentage of women eligible for LEEP or suspicious cancer who have access to histopathological diagnosis	50%
	Surgical treatment rate for invasive cancer	10% of eligible women
	Radiotherapy and chemotherapy treatment	65%
	VIAC outreach services	
	CC age-specific mortality rate	from 35.3-33/100,000
	CC age-specific incidence	from 56.4-52/100,000

Guidelines For ART for the Prevention and Treatment of HIV	Number of people trained	
	Percentage of people trained still working in the content area 1 year later	
	Percentage of facilities offering VIA and cryotherapy	
	Number of district, provincial and national awareness campaigns	
	Number of Mass screening campaigns	
	Number of new women who received VIA screening in the target age range	
South Africa		
Cervical Cancer Prevention and Control Policy	Coverage of HPV vaccination (defined)	
	Incidence of oncogenic HPV infection	
	Proportion of primary health care facilities providing LBC	
	Availability of LBC services	
	Access to CC screening services	
	PHC that can provide cervical cancer screening services	
	Coverage of CC screening amongst eligible women	
	Total number of women with HG SIL	
	Treatment of precancerous lesions. Women with HG- SIL / CIN 2-3 who receive appropriate treatment	
	Proportion of women with cervical cancer still living 5 years from date of diagnosis	
	Incidence of cervical cancer	
	Mortality of CC	reduce by 20%
	5-year survival of women diagnosed with CC	
	Women with cervical cancer who receive palliative care	
Strategic Plan for the Prevention and Control of NCDs	Number of pre-sexual girls given the HPV vaccine	All age appropriate girls 100%

	Number of women with STIs screened for CC at diagnosis and every 5 years and Number of other screened women every 10 years.	65% of women over 30 attending public sector clinics screened. 65% of women with STIs screened soon after/at diagnosis at the 5 year intervals
Mozambique		
National Cancer Control Plan	Create health indicators that allow monitoring and evaluation of cancer care	
National Guidelines for the Prevention Of Cervical Cancer	Screening coverage rate:	80%
	Number VIA positive	VIA negative
	Number VIA positive by HIV status	Provider's ability to diagnose and recommend the correct treatment by observing images of the cervix
Namibia		
National Multisectoral Strategic Plan for Prevention and Control of NCDs	Coverage of vaccination against human papillomavirus (HPV) among girls aged 11 - 13 years	95%
	Coverage of cervical cancer screening for women between ages 30-49 years	80%-2025
	Access to palliative care assessed by morphine equivalent consumption of strong opioid analgesics (excluding methadone) per death from cancer	20% increase-2025
	Mortality from NCDs	
	Proportion of complications	
	Proportion of women living with HIV 30−49 years old who report being screened for cervical cancer using any of the following methods: visual inspection with acetic acid or vinegar (VIA), Pap smear or human papillomavirus (HPV) test	70% by 2022
National Cervical Cancer Prevention Guidelines	Numbers of women screened using VIA, Pap smear, and HPV testing	
	Percentage of eligible women screened	

	Numbers and percentages of women screened, by (five-year) age bracket	
	Numbers and percentages of women screened, by HIV status (positive, negative, unknown)	
	Number of women with abnormal screening results, disaggregated by HIV status	
	Number of women with abnormal screening results who receive treatment, disaggregated by HIV status	
	Number of health care facilities providing cervical cancer screening, and the screening methods provided	
	Number of health care workers trained in VIA and treatment procedures	
	Number of new clients with suspected cancer	
	Number of clients with suspected cancer referred	
	Number of clients with suspected cancer who were seen and evaluated	
	Number of clients who had confirmed cervical cancer	
	Number of clients treated for cervical cancer	
Botswana		
National Multi-sectoral Strategy for the Prevention and Control of NCDs	Coverage of HPV vaccination within eligible population 11-13	95%-2022, 98% 2025
	CC screening coverage 30-49 years	80%-2022 - 70%Pap, 30% VIA
	Percentage screened and linked to care	
	Treatment of key cancers compliant with treatment guidelines	80%-2022
	Opiate consumption	30% increase-2022
	Number of policy changes resulting from research findings	
	Average referral scheduling wait times for suspected cancer	
	Number of stakeholders reporting on NCD indicators, % completeness and timeliness of core NCD indicators	
	Number of key NCD data fields integrated into existing health information systems infrastructures	
	Number of national registries established for all major NCDs (hypertension, diabetes, heart disease, cancer)	

	Incidence of CC	
	Percentage of CC diagnosed early	60%-2025
	Access to palliative care per capita morphine consumption)	
	30% increase in opiate consumption	
	Achievement of 80% in set targets of training NCD-relevant specialists by 2025	
	Proportion of cervical and breast cancers diagnosed early	
	Proportion of population with NCD prevention information (awareness)	
	National (multi-sectoral) per capita spending on NCDs	
Integrated Health Service Plan	Proportion of women screened for cervical cancer	
	Number of cases of CC by stage	
	Incidence of CC	
Comprehensive Prevention and Control Strategy	Vaccination coverage	
National Cervical Cancer Prevention Programme	Number and percentage of women screened among eligible women	80%
	Number and percentage of women with abnormal results	
	Number and percentage of women with abnormal results who receive treatment	
	Number and percentage of cervical cancer patients referred for palliative care	
	Number and percentage of cervical cancer patients receiving palliative care	
	Number and percentage of health facilities providing palliative care services	

Table S9. List of documents reviewed

Country	Plan title	Year (period)	Source
Botswana	Botswana National Multi-sectoral Strategy for the Prevention and Control of Non-Communicable Diseases	2018-2023	ICCP portal
	Integrated health service plan: Strategy for Changing the Health Sector For Healthy Botswana	2010-2020	Google/Expert
	Five-year Comprehensive Prevention and Control Strategy National Cervical Cancer Prevention Programme, Botswana	2012-2016	Expert
Eswatini	National cancer prevention and control strategy The National Cancer Control Plan	2019-2022	ICCP portal
	Sexual and reproductive health - Annual Program Report	2018	Expert
	National Prevention and Control of NCDs - annual programme report	2018	Expert
Lesotho	National multi-sectoral integrated strategic plan for the prevention and control of NCDs	2014-2020	ICCP portal
	National health strategic plan	2017-2022	Expert
	Clinical practice standards: CC prevention. CC prevention practice guidelines	2015	Expert
	Guidelines for screening for cervical pre-cancer in Lesotho	2012	Expert
	Guidelines for screening for Cervical Pre-cancer in Lesotho	2020	Expert
Malawi	National Cervical Cancer control strategy	2016-2020	ICCP portal
	Standard Operating Procedures (SOP) for CC services	developed-2019	Expert
	National service delivery guidelines for CC prevention and control	developed-2019	Expert
	Malawi National Cancer Control strategic plan	2019-2029	ICCP portal
	Malawi Cervical Cancer Strategic plan	2022-2026	Expert
Mozambique	National Cancer Control plan	2019-2029	Expert
	National guidelines for the prevention of cervical cancer	Not stated	Expert

Namibia	National Multi sectoral Strategic Plan For Prevention and Control of NCDs in Namibia	2017/18-2021/22	ICCP portal
	National strategic framework for HIV/AIDS response in Namibia	2017-2022	Expert
	National Cervical Cancer Prevention Guidelines, Namibia	2018	Expert
	National Health Policy Framework	2010-2020	Expert
South Africa	Cervical cancer prevention and control policy	2017	Google
	National cancer strategic framework for south Africa	2017-2022	Google
	South Africa NCD strategic plan	2013-2017	ICCP portal
Zambia	National cancer control strategic plan	2016-2021	Expert
	Zambia Consolidated guidelines for treatment and prevention of HIV	2018	Expert
	Visual Inspection with Acetic Acid and Cryotherapy - A Reference Manual for Trainers and health Care Providers	2015	Expert
Zimbabwe	National cancer prevention and control strategy for Zimbabwe	2014-2018	ICCP portal
	The Zimbabwe cervical cancer prevention and control strategy	2016-2020	Expert
	Guidelines for ART for the prevention and treatment of HIV in Zimbabwe	2016	Expert
	Final Addendum to the 2016 ART Guidelines	2019	Expert
	National STI Guideline	2019	Expert

Table S10. Age standardised cervical cancer incidence and mortality rates for included countries

Country	Incidence rate/100,000 women-years	Mortality rate/100,000 women-years
Botswana	34.4	20.1
Eswatini	84.5	55.7
Lesotho	56.8	38.7
Malawi	67.9	51.5
Mozambique	50.2	38.7
Namibia	37.4	22.5
South Africa	35.3	19.6
Zambia	65.5	43.4
Zimbabwe	61.7	43.0

***Source**: HPV information centre (https://hpvcentre.net/datastatistics.php), 2021*

11.3. Supplementary Information Publication 3

Asangbeh-Kerman SL, **Davidović M**, Taghavi K, et al; International Epidemiology Databases to Evaluate AIDS. Cervical cancer prevention and care in HIV clinics across sub-Saharan Africa: results from a facility-based survey. J Int AIDS Soc. 2024 Jul;27(7):e26303

The supplementary information is available from: https://doi.org/10.1002/jia2.26303, accessed July 14, 2024.

Table of content

Table S1. HPV vaccination

Region (number of sites)	Central Africa (n=7)	East Africa (n=8)	Southern Africa (n=9)	West Africa (n=6)	**Total (N=30)**
Variables	N (%)	N (%)	N (%)	N (%)	**N (%)**
HPV vaccination					
Yes, ongoing	5 (50)	3 (30)	2 (20)	0 (0)	**10 (33)**
Yes, in the past	0 (0)	2 (29)	3 (43)	2 (29)	**7 (23)**
No	2 (15)	3 (23)	4 (31)	4 (31)	**13 (43)**
Reason HPV vaccination was stopped	**n=0**	**n=2**	**n=3**	**n=1**	**N=7**
Lack of funding	0 (0)	1 (33)	1 (33)	1 (33)	**3 (43)**
Vaccination is given once a year	0 (0)	0 (0)	2 (100)	0 (0)	**2 (29)**
COVID-19 and low community acceptance	0 (0)	1 (100)	0 (0)	0 (0)	**1 (14)**
Research project	0 (0)	0 (0)	0 (0)	1 (100)	**1 (14)**
HPV vaccination in sites with ongoing or past programs	**n=5**	**n=5**	**n=5**	**n=2**	**N=17**
Vaccination strategy					
School-based only	0 (0)	2 (67)	1 (33)	0 (0)	**3 (10)**
School and Community-based	4 (67)	0 (0)	2 (33)	0 (0)	**6 (20)**
School-, community-based and Campaigns	1 (100)	0 (0)	0 (0)	0 (0)	**1 (3)**
Campaigns only	0 (0)	0 (0)	0 (0)	1 (100)	**1 (3)**
Routine	0 (0)	3 (75)	1 (25)	0 (0)	**4 (13)**
Not applicable/missing	2 (13)	3 (20)	4 (27)	6 (40)	**15 (50)**
HPV vaccine type					
Bivalent	0 (0)	0 (0)	2 (50)	2 (50)	**4 (24)**
Quadrivalent	5 (50)	4 (40)	1 (10)	0 (0)	**10 (59)**
Nonavalent	0 (0)	0 (0)	1 (100)	0 (0)	**1 (6)**
Unknown	0 (0)	1 (50)	1 (50)	0 (0)	**2 (12)**
Target population					
Girls only	5 (31)	5 (31)	4 (25)	2 (13)	**16 (94)**
Girls and boys	0 (0)	0 (0)	1 (100)	0 (0)	**1 (6)**
Target age					
< 15 years old	5 (31)	5 (31)	4 (25)	2 (13)	**16 (94)**
8-18 years old	0 (0)	0 (0)	1 (11)	0 (0)	**1 (6)**
HPV vaccination free of charge					
Yes	5 (29)	5 (29)	5 (29)	2 (12)	**17 (100)**

Abbreviation: HPV, Human Papillomavirus. Total percentages are column percentages in bold, and percentages per region are row percentages

Table S2. Cervical cancer diagnosis and treatment/management

Region (number of sites)	Central Africa	East Africa	Southern Africa	West Africa	**Total**
Variables	N = 7 (%)	N = 8 (%)	N = 9 (%)	N = 6 (%)	**N=30 (%)**
Cancer diagnosis					
Histopathology	1 (8)	3 (25)	4 (33)	4 (33)	**12 (40)**
Biopsy sent to South Africa	0 (0)	0 (0)	1 (100)	0 (0)	**1 (3)**
Referred	0 (0)	2 (100)	0 (0)	0 (0)	**2 (7)**
Clinical	0 (0)	0 (0)	0 (0)	2 (100)	**2 (7)**
Tomodensitometry	0 (0)	0 (0)	0 (0)	1 (100)	**1 (3)**
Not available	3 (38)	2 (25)	3 (38)	0 (0)	**8 (27)**
Cancer treatment					
Simple hysterectomy	1 (9)	4 (36)	2 (18)	4 (36)	**11 (37)**
Radical hysterectomy	2 (13)	5 (31)	3 (19)	6 (38)	**16 (53)**
Chemotherapy	1 (8)	4 (31)	3 (23)	5 (39)	**13 (43)**
Radiation therapy	0 (0)	5 (42)	2 (17)	5 (42)	**12 (40)**
Intra-cavitary radiation	0 (0)	0 (0)	2 (50)	2 (50)	**4 (13)**
None	3 (30)	2 (20)	5 (50)	0 (0)	**10 (33)**
Access to opioids					
Always	0 (0)	1 (17)	3 (50)	2 (33)	**6 (20)**
Sometimes	1 (33)	2 (67)	0 (0)	0 (0)	**3 (10)**
Never	6 (30)	4 (20)	6 (30)	4 (20)	**20 (67)**

Note: Total percentages are column percentages in bold, and percentages per region are row percentages.

Table S3. Laboratory testing and Quality Assurance

Region (number of sites)	Central Africa	East Africa	Southern Africa	West Africa	**Total**
Variables	N = 7 (%)	N = 8 (%)	N = 9 (%)	N = 6 (%)	**N = 30 (%)**
Laboratory testing					
Laboratory testing for pre-cancer only					
Yes	0 (0)	1 (20)	2 (40)	2 (40)	**5 (29)**
Laboratory testing (diagnosis) for invasive cancer only					
Yes	0 (0)	0 (0)	2 (100)	0 (0)	**2 (12)**
Laboratory testing (diagnosis) for both pre-cancer and invasive cancer					
Yes	0 (0)	4 (40)	3 (30)	3 (30)	**10 (59)**
Time between sample collection and arrival at laboratory					
1 day	0 (0)	2 (29)	2 (29)	3 (43)	**7 (41)**
2-7 days	0 (0)	2 (29)	5 (71)	0 (0)	**7 (41)**
Same day HPV, 2 weeks for cytology and histopathology	0 (0)	0 (0)	0 (0)	1 (100)	**1 (6)**
No specific time	0 (0)	1 (100)	0 (0)	0 (0)	**1 (6)**
Sample collection in laboratory	0 (0)	0 (0)	0 (0)	1 (100)	**1 (6)**
Results turn- around time					
Same day for HPV/ 2 months for cytology and histology	0 (0)	0 (0)	0 (0)	1 (100)	**1 (7)**
<1 week	0 (0)	1 (50)	1 (50)	0 (0)	**2 (13)**
1-4 weeks	0 (0)	3 (27)	5 (45)	3 (27)	**11 (65)**
5-6 weeks	0 (0)	1 (33)	1 (33)	1 (33)	**3 (20)**
Results reception format					
Electronic	0 (0)	2 (29)	3 (43)	2 (29)	**7 (23)**
Paper format	2 (11)	4 (22)	7 (39)	5 (28)	**18 (60)**
Transfer of results					
Results are sent to clinic	2 (14)	3 (21)	6 (43)	3 (21)	**14 (47)**
Staff actively go search for them	0 (0)	2 (33)	2 (33)	2 (33)	**6 (20)**
Time between results reception and communication to client					

Within 7 days	0 (0)	5 (42)	4 (33)	3 (25)	**12 (40)**
Women asked to return in 2 weeks	0 (0)	0 (0)	1 (100)	0 (0)	**1 (3)**
About 30 days (during next HIV appointment)	0 (0)	0 (0)	2 (100)	0 (0)	**2 (7)**
Quality Assurance					
Quality assurance policy or guideline available					
Yes	2 (14)	6 (43)	3 (21)	3 (21)	**14 (48)**
No	3 (33)	0 (0)	3 (33)	3 (33)	**9 (30)**
Unknown	2 (33)	1 (17)	3 (50)	(0)0	**6 (21)**
Quality assurance coordinator or team available					
Yes	1 (6)	7 (41)	6 (35.3)	3 (18)	**17 (59)**
No	4 (44)	(0) 0	2 (22)	3 (33)	**9 (31)**
Unknown	2 (67)	(0) 0	1 (33)	(0)0	**3 (10)**
System of accreditation for HPV					
Yes	0(0)*	5 (50)	5 (50)	(0)0	**10 (33)**
No	5 (31)	2 (13)	3 (19)	6 (38)	**16 (53)**
Unknown	1 (50)	(00	1 (50)	(0)0	**2 (7)**
System of accreditation for pathology					
Yes	1 (17)	1 (17)	3 (50)	1 (17)	**6 (20)**
No	4 (27)	3 (20)	4 (27)	4 (27)	**15 (50)**
Unknown	2 (25)	3 (38)	2 (25)	1 (13)	**8 (27)**

Abbreviation: HPV, Human Papillomavirus. Total percentages are column percentages in bold, and percentages per region are row percentages.

Table S4. Referral and tracking

Region (number of sites)	Central Africa	East Africa	Southern Africa	West Africa	**Total**
Variables	N = 7 (%)	N = 8 (%)	N = 9 (%)	N = 6 (%)	**N=30 (%)**
SCREENING					
Referral for screening					
Always	5 (71)	1 (14)	1 (14)	0 (0)	**7 (23)**
Sometimes	2 (11)	4 (22)	6 (33)	6 (33)	**18 (60)**
Never	0 (0)	2 (67)	1 (33)	0 (0)	**3 (10)**
Missing	0 (0)	1 (3)	1 (3)	0 (0)	**2 (7)**
Receiving site for referral					
On-site	3 (30)	3 (30)	3 (30)	1 (10)	**10 (33)**
Off-site	4 (31)	2 (15)	3 (23)	4 (31)	**13 (43)**
Missing	0 (0)	0(0)	1 (50)	1(50)	**2 (7)**
Not applicable	0 (0)	3 (60)	2 (40)	0 (0)	**5 (17)**
Reason for screening referral*					
Screening services available in another unit in hospital	3 (33)	2 (22)	3 (33)	1 (11)	**9 (38)**
Screening services available but not always functional	0 (0)	0 (0)	0 (0)	1 (100)	**1 (4)**
Screening services not available on-site	2 (50)	0 (0)	1 (25)	1 (25)	**4 (17)**
For diagnosis (suspect cancer)	2 (20)	3 (30)	2 (20)	3 (30)	**10 (42)**
Missing	0 (0)	0 (0)	1 (100)	0 (0)	**1(3)**
Do you keep track of women referred for screening?					
Always	3 (17)	5 (28)	6 (33)	4 (22)	**18 (60)**
Sometimes	2 (40)	0 (0)	1 (20)	2 (40)	**5 (17)**
Never	2 (33)	2 (33)	2 (33)	0 (0)	**6 (20)**
Missing	0 (0)	1 (100)	0 (0)	0 (0)	**1 (3)**
Tracing strategy					
Phone call	1 (8)	3 (25)	4 (33)	4 (33)	**12 (48)**
Trace from HIV clinic	3 (30)	2 (20)	3 (30)	2 (20)	**10 (33)**
Missing	3 (100)	0 (0)	0 (0)	0 (0)	**3 (10)**

Not applicable	0 (0)	3 (60)	2 (40)	0 (0)	**5 (17)**
Trace lab results not received					
Always	0 (0)	5 (31)	6 (38)	5 (31)	**16 (94)**
Sometimes	0 (0)	0 (0)	1 (100)	0 (0)	**1 (6)**
Not applicable	7 (54)	3 (23.0)	2 (15)	1 (8)	**13 (43)**
Tracing strategy					
Send a query to the lab	0 (0)	4 (31)	6 (46)	3 (23)	**13 (77)**
Re-invite women for screening	0 (0)	0 (0)	1 (50)	1 (50)	**2 (12)**
Visit the laboratory	0 (0)	0 (0)	0 (0)	1 (100)	**1 (6)**
Repeat Pap smear	0 (0)	0 (0)	1 (100)	0 (0)	**1 (6)**
Not applicable	7 (54)	3 (23)	2 (15)	1 (8)	**13 (43)**
PRE-CANCER					
Do you contact women for pre-cancer treatment?					
Always	2 (12)	5 (29)	4 (24)	6 (35.3)	**17 (57)**
Sometimes	1 (20)	1 (20)	3 (60)	0 (0)	**5 (17)**
Never	3 (50)	1 (17)	2 (33)	0 (0)	**6 (20)**
Missing	1 (50)	1 (50)	0 (0)	0 (0)	**2 (7)**
Do you refer women for pre-cancer treatment?					
Always	4 (33)	3 (25)	1 (8)	4 (33)	**12 (40)**
Sometimes	1 (8)	3 (23)	7 (54)	2 (15)	**13 (43)**
Never	2 (50)	1 (25)	1 (25)	0 (0)	**4 (13)**
Missing	0 (0)	1 (100)	0 (0)	0 (0)	**1 (3)**
Reasons for pre-cancer treatment referral					
No treatment infrastructure	3 (33)	2 (22)	1 (11)	3 (33)	**9 (30)**
Large lesion/suspect cancer	1 (8)	3 (25)	5 (42)	3 (25)	**12 (40)**
Need for specialised care	0 (0)	1 (50)	1 (50)	0 (0)	**2 (7)**
Missing	1	0 (0)	1	0 (0)	**2 (7)**
Not applicable	2	1	1	0 (0)	**5 (17)**
Contact for follow-up after pre-cancer treatment					
Always	1 (7)	5 (33)	4 (27)	5 (33)	**15 (50)**
Sometimes	2 (29)	2 (29)	3 (43)	0 (0)	**7 (23)**
Never	4 (57)	0 (0)	2 (29)	1 (14)	**7 (23)**

Missing	0 (0)	1 (100)	0 (0)	0 (0)	**1 (3)**
CERVICAL CANCER					
Do you contact women for cancer treatment?					
Always	2 (14)	5 (36)	3 (21)	4 (29)	**14 (47)**
Sometimes	2 (33)	1 (17)	1 (17)	2 (33)	**6 (20)**
Never	2 (25)	1 (13)	5 (63)	0 (0)	**8 (27)**
Missing	1 (50)	1 (50)	0 (0)	0 (0)	**2 (7)**
Referral for cancer treatment					
Always	3 (14)	5 (24)	7 (33)	6 (29)	**21 (70)**
Sometimes	1 (20)	2 (40)	2 (40)	0 (0)	**5 (17)**
Never	3 (43)	0 (0)	0 (0)	0 (0)	**3 (10)**
Missing / unknown	0 (0)	1 (100)	0 (0)	0 (0)	**1 (3)**
Reasons for cancer treatment referral					
No treatment infrastructure	3 (21)	3 (21)	5 (36)	3 (21)	**14 (47)**
Need for specialised care	0 (0)	4 (40)	3 (30)	3 (30)	**10 (33)**
Missing	1 (50)	0 (0)	1 (50)	0 (0)	**2 (7)**
Not applicable	3 (75)	1 (25)	0 (0)	0 (0)	**4 (13)**
Contact for follow-up after cancer treatment					
Always	1 (9)	5 (46)	1 (9)	4 (36)	**11 (37)**
Sometimes	1 (20)	1 (20)	3 (60)	0 (0)	**5 (17)**
Never	5 (39)	1 (8)	5 (39)	2 (15)	**13 (43)**
Missing	0 (0)	1 (100)	0 (0)	0 (0)	**1 (3)**

Note: total percentages are column percentages in bold, and percentages per region are row percentages.

Table S5. Facility characteristics associated with the availability of CC data for WLHIV

CC data for WLHIV available	Facility characteristics			p-value
Facility location				
	Rural	Urban	-	
Yes	2 (18)	9 (82)	-	1.00
No	1 (9)	10 (91)	-	
Missing	2 (25)	6 (75)	-	
Facility type				
	Public	NGO	Other	
Yes	8 (73)	3 (27)	0 (0)	0.32
No	8 (73)	1 (9)	2 (18)	
Missing	6 (75)	1 (13)	1 (13)	
Services integration				
	In another unit within HIV clinic premises	Within HIV clinic	Off-site	
Yes	3 (27)	8 (73)	0 (0)	0.12
No	6 (55)	3 (27)	2 (18)	
Missing	4 (50)	4 (50)	0 (0)	
NGO support for CC prevention				
	Yes	No		
Yes	8 (73)	3 (27)	-	**0.03**
No	2 (17)	9 (82)	-	
Missing	3 (38)	5 (63)	-	

Table S6. HPV Vaccination in sites with data for girls living with HIV

Region	**Central Africa**		**East Africa**	**Southern Africa**
Country Name	Rwanda		Tanzania	Zimbabwe
Facility Name	Gikondo HC	Masaka HC	Kisesa HC	Newlands Clinic
Index yea	2018	2018	-	2019
Eligibility criteria (age in years)	10-14	12	-	8-18
# of eligible girls	4	2	25	24
# of eligible young women (15-26 years)	4	62	32	3
Vaccinated against HPV before 15 years old	4 (100)	2 (100)	22 (88)	5 (21)
Vaccinated against HPV after 15 years old	-	2 (3)	29 (91)	2 (67)

Abbreviations: HC, Health Centre; #, number

Table S7. Cervical screening

Region and Facility Name	Index year	Women in care	Screened		Screen negative		Screen positive		First time screen		First time screen positive		Inconclusive results	
	Calendar year	N	N	Rate [%][a]	N	Rate [%][b]	N	Rate [%][c]	N	Rate [%][d]	N	Rate [%][e]	N	Rate [%][f]
Data for WLHIV														
Central Africa														
Kabuga HC	-	-	-		-		-		-	-	-	-	-	-
East Africa														
Tumbi Regional Referral Hospital	2020	2158	422	20	-		5	1.2	-	-	-	-	-	-
Infectious Diseases Institute	2015	5264	548	10	484	88	60	11	-	-	41	-	-	-
Southern Africa														
Seboche Mission Hospital	-	-	-	-	-		-		-	-	-	-	-	-
Lighthouse Trust	2020	10681	4881	46	4234	87	124	3	-	-	73	-	-	-
Kanyama	2020	6416	4438	69	3343	75	1040	23	-	-	-	-	-	-
George HC	2020	419	3731	g	3575	96	136	4	-	-	-	-	-	-
Newlands Clinic	2019	3759	2924	78	2624	90	276	9	233	6	47	20	0	-
West Africa														
CEPREF Yopougon	2017	3819	485	1	371	77	111	2	-	-	111	-	0	-
CNTS - Public-Ko'khoua	2019	1520	702	46	674	96	28	4	-	-	-	-	-	-
Hôpital de Jour Du Chu Souro Sanou	2019	3302	142	4	94	66	48	3	-	-	-	-	0	-
All available data (including women without HIV and/or women referred from other health facilities)														
Central Africa														
Busanza HC	2020	318	-		-		-		-	-	-	-	-	-
Gikondo HC	2018	1146	20	2	-		3	15	-	-	-	-	-	-
Masaka HC	2018	558	-		-		-		-	-	-	-	-	-
Nyarugunga HC	2019	367	2		-		2	100	-	-	-	-	-	-
East Africa														

MOI Teaching And Referral Hospital	2018	5174	5174	100	4865	94.0	308	6	-	-	193	-	1	0.2
Lumumba hospital	2018	4721	0		0		0		-	-	0	-	0	-
Morogoro hospital	2020	2421	926	38	-		57	6	-	-	0	-		-
Masaka Regional Referral Hospital	2019	8931	46	1	0		5	11	-	-	0	-	0	-
Southern Africa														
Rahima Moosa MCH	2020	271	-		-		-		-	-	-	-	-	-
Chongwe rural HC	2020	286	1510	h	1093	72.4	99	7	-	-	0	-	0	-
Chiure Hospital	-	-	293	-	-		33	13	-	-	-	-	-	-
Ngwerere rural HC	2020	524	346	66	409	h	12	2	-	-	12	-	0	-
West Africa														
CIRBA	2018	1674	251	15	251	100	0	0	-	-	0	-	0	-
Nigerian Institute Of Medical Research	2017	5567	1449	26	1264	87	180	12	-	-	154	11	5	0.3
USAC	2016	1988	409	20	399	98	10	2	-	-	5	1	0	-

Abbreviations: HC – Health centre; CEPREF – «Centre d'Excellence de Prise en charge des patients du VIH/SIDA», CNTS – «Centre National de Transfusion Sanguine», CIRBA – «Centre Intégré de Recherches Biocliniques d'Abidjan», USAC – «Unité de Soins Ambulatoires et de Conseil »; MCH – Mother and Child Hospital.

[a]Number screened/Number of women in care, [b]Number screened negative/Number screened, [c]Number screened positive/Number screened, [d]Number screened for first time/Number screend, [e]Number screened positive for first time/Number screened, [f]Number with inconclusive results/Number screened, [g]percentage greater than 100 (528) due to referrals for screening, [g,h]Percentage greater than 100 (118) due to referrals for screening

Table S8. Treatment of pre-cancerous lesions: rates according to changing denominators

Region and Facility name	Screen positive		Treated		Treatment postponed		Postponed treatment received		Referred for treatment		Received treatment after referral		Post treatment complications		Precancer cure rate	
	n	Rate [%][a]	n	Rate [%][b]	n	Rate [%][c]	n	Rate [%][d]	n	Rate [%][e]	n	Rate [%][f]	n	Rate [%][g]	n	Rate [%][h]
Data for WLHIV in care																
East Africa																
Tumbi Regional Referral Hospital	5	1.2	-	-	-	-	-	-	-		-	-	-		-	-
Infectious Diseases Institute	60	11	-	-	-	-	-	-	40	67	-	-	-		-	-
Southern Africa																
Lighthouse Trust	124	2.5	58	47	-	-	-	-	-		-	-	-		-	-
Chiure Hospital	33	13	-	-	-	-	-	-	-		-	-	-		-	-
Kanyama	1040	23	143	14	0	0	0	0	118	11	0	0	0	0	1	0.7
George Health Centre	136	3	136	100	4	3	4	100	59	43	59	100	0	0	15	11
Newlands Clinic	276	9	268	97	18	7	18	100	258	94	244	95	0	0	167	62
West Africa																
CEPREF Yopougon	111	22.9	85	77	5	4.5	5	100	26	23	-	-	0	0	106	i
CNTS- Public-Ko'khoua	28	52	-	-	-		-	-	-		-	-	-		-	-
Hôpital De Jour Du CHU Souro Sanou	48	34	24	50	6	13	-	-	6	13	-	-	0	0	-	-
All available data (including women without HIV and women referred from other health facilities)																
Central Africa																
Gikondo HC	3	15	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nyarugunga HC	2	100	-	-	-	-	-	-	-	-	-	-	-	-	-	-
East Africa																
Moi Teaching and Referral Hospital	308	88	45	15	0	0	0	0	0	0	0	0	3	7	42	93
Lumumba Hospital	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0

Hospital	57	6	-	-	-		1	-	0	0	0	0	0	0	0	0
Masaka Regional Referral Hospital	5	11	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Southern Africa																
Chongwe rural HC	99	7	12	12	-	-	0	0	67	68	0	0	0	0	0	0
Ngwerere Rural Health Centre	69	15	11	16	0	0	-	-	1	2	0	0	-	-	4	36
CIRBA	7	3	0	0	-	-	-	-	-	-	-	-	-	-	-	-
West Africa																
Nigerian Institute Of Medical Research	180	12	-	-	3	2	0	0	180	100	-	-	-		-	-
USAC	10	2	10	100	0	0	-	0	10	100	8	80	0	0	8	80

Abbreviations: HC – Health centre; CEPREF – «Centre d'Excellence de Prise en charge des patients du VIH/SIDA», CNTS – «Centre National de Transfusion Sanguine»,CIRBA – «Centre Intégré de Recherches Biocliniques d'Abidjan», USAC – «Unité de Soins Ambulatoires et de Conseil»; CHU – «Centre Hospitalier Universitaire»

[a]Number screened positive/Number of women in care, [b]Number treated/Number screened positive, [c]Number with treatement postponed/Number screened positive, [d]Number who received treatment after being postponed/Number with treatment postponed, [e]Number referred for treatment/Number screened positive, [f]Number who received treatement after refferral/Number referred for treatment, [g]Number with post treatment complications/Number treated , [h]Number free from precaner at follow-up/Number treated, [i]Percentage greater than 100 (124.7) due to referrals for post-treatment follow-up.

Table S9. Cervical cancer diagnosis and management

Region and Facility Name	Screen positive		Suspicious CC		Diagnosed for CC		Confirmed CC		CC Management	
Data for WLHIV in care										
	n	Rate [%][a]	**n**	Rate [%][b]	**n**	Rate [%][c]	**n**	Rate [%][d]	**n**	Rate [%][e]
East Africa										
Tumbi Regional Referral Hospital	5	1	-	-	-	-	-	-	0	0
Infectious Diseases Institute	60	11	0	-	2	-	0	-	0	0
Southern Africa										
Chiure Hospital	33	13	-	-	-	-	-	-	-	-
Kanyama	1040	23	10	1	0	0	0	-	0	-
George Health Centre	136	4	20	15	0	0	0	-	0	-
Newlands Clinic	276	9	4	44	5	f	3	75	3	100
Lighthouse Trust	124	2.5	17	14	-	-	-	-	-	-
West Africa										
CEPREF Yopougon	111	22.9	3	2.7	3	100	3	100	-	-
CNTS - Public-Ko'khoua	28	52	-	-	-	-	-	-	-	-
Hôpital de Jour du CHU Souro Sanou	48	33.8	2	4	48	100	1	6	1	100
All available data (including women without HIV and women referred from other health facilities)										
Central Africa										
Gikondo Health Center	3	15	-	-	-	-	-	-	-	-
Nyarugunga Health Center	2	100	-	-	-	-	-	-	-	-
East Africa										
Moi Teaching And Referral Hospital	308	88	164	53	193	g	141	73	342	h

Lumumba Hospital	0	0	0	0	0	-	0	0	0	0
Morogoro Hospital	57	6	0	0	0	-	0	0	0	0
Masaka Regional Referral Hospital	5	11	0	0	0	-	0	-	0	0
Southern Africa										
Chongwe Rural HC	99	7	8	8	0	-	0	-	0	0
Ngwerere Rural Health Centre	69	15	1	8	0	-	0	-	-	-
Newlands Clinic	276	9	4	1	5	i	3	75	3	100
West Africa										
CIRBA	7	3	-	-	-	-	0	-	-	-
Nigerian Institute of Medical Research	180	12	5	3	29	j	2	50	4	200
USAC	10	2	2	20	-	-	-	-	0	0

Abbreviations: HC – Health centre; CEPREF – «Centre d'Excellence de Prise en charge des patients du VIH/SIDA», CNTS – «Centre National de Transfusion Sanguine»,CIRBA – «Centre Intégré de Recherches Biocliniques d'Abidjan», USAC – «Unité de Soins Ambulatoires et de Conseil»; CHU – «Centre Hospitalier Universitaire»; CC – cervical cancer

[a]Number screened positive/Number of women in care, [b]Number with suspected CC/Number screened positive, [c]Number with diagnosis of CC performed/Number with suspected CC, [d]Number with confirmed CC/Number with diagnosis performed for CC, [e]Number with ICC managed/Number with confirmed CC, [f]Percentage greater than 100 (118) due to referrals for CC diagnosis, [g,h,i,j] Rate higher than 100% due to referrals for CC diagnosis and management from other sites.

Table S10. Referral for diagnosis and treatment of cervical cancer

Region and Facility Name	Screen positive		Suspected CC		Referred for suspected cancer		Diagnosed after referral		Treated after referral	
	N	Rate [%][a]	N	Rate [%][b]	N	Rate [%][c]	N	Rate [%][d]	N	Rate [%][e]
East Africa										
Moi Teaching and Referral Hospital	308	88	164	53	0	0	0	0	0	0
Lumumba hospital	0	0	0	0	0	0	0	0	0	0
Morogoro Hospital	57	6	0	0	7	-	0	0	0	0
Infectious Diseases Institute	60	11	0	0	-	-	-	-	-	-
Masaka Regional Referral Hospital	5	11	0	0	0	0	0	0	0	0
Southern Africa										
Lighthouse Trust Martin Preuss Center	124	3	17	14	-	-	-	-	-	-
Chiure hospital	33	13	-	-	-	-	-	-	-	-
Chongwe Rural HC	99	7	8	8	8	100	0	0	0	0
Kanyama	1040	23	10	1	10	100	0	0	0	0
Ngwerere rural health centre	69	15	1	8	1	100	0	0	0	0
George health centre	136	4	20	15	20	100	0	0	0	0
Newlands Clinic	276	9	4	1	4	100	2	50	1	50
West Africa										
CIRBA	7	3	-	-	-		-	-	-	-
CEPREF Yopougon	111	23	3	3	3	100	3	100	-	-
Institute of Medical Research, Lagos, Nigeria	180	12	5	3	2	40			-	-
Hôpital de Jour du CHU Souro Sanou	48	34	2	4	2	100	1	50	1	100
USAC	10	2	2	20	2	100	-	-	-	-

Abbreviations: HC – Health centre; CEPREF – «Centre d'Excellence de Prise en charge des patients du VIH/SIDA»; CIRBA – «Centre Intégré de Recherches Biocliniques d'Abidjan»; USAC – «Unité de Soins Ambulatoires et de Conseil»; CHU – «Centre Hospitalier Universitaire»; ICC – Invasive Cervical Cancer

[a]Number screened positive/Number of women in care, [b]Number with suspected CC/Number screened positive, [c]Number with suspected CC referred/Number with suspected CC, [d]Number diagnosed with CC after referral/Number with suspected CC referred, [e]Number with CC managed after referral/Number diagnosed with CC after referral.

Table S11. Number of women screened by type of test

Region and Facility Name	# screened VIA	Screen-positive VIA	# screened VIAC	Screen-positive VIAC	# screened VILI	Screen-positive VILI	# screened Pap	Screen-positive Pap	# screened HPV DNA	Screen-positive HPV DNA
Data for WLHIV in care										
East Africa										
Tumbi Regional Referral Hospital	422	5	0	5	0	0	0	0	0	0
Infectious Diseases Institute	548	63	0	0	0	0	0	0	0	0
Southern Africa										
Lighthouse Trust	4881	124	-	-	-	-	-	-	253	-
Chiure hospital	293	33	0	0	0	0	0	0	0	0
Kanyama	2504	152	0	0	0	0	0	0	-	1934
George health centre	3731	156	156	156	0	0	0	0	19	1
West Africa										
CEPREF Yopougon	482	114	485	114	111	114	0	0	0	0
CNTS - Public-Ko'khoua	702	28	702	28	702	28	-	-	-	-
Hopital de Jour CHU Souro Sanou	47	25	47	25	47	25	0	0	142	48
All available data (including women without HIV and women referred from other health facilities)										
Central Africa										
Gikondo HC	20	3	-	-	-	-	-	-	-	-
Nyarugunga HC	2	2	226	2	-	-	-	-	-	-
East Africa										
MOI Teaching and Referral Hospital	5174	308	0	0	0	0	28		0	0
Morogoro Hospital	926	57	0	0	0	0	0	0	0	0
Masaka Regional Referral Hospital	46	5	0	0	0	0	4	4	0	0
Southern Africa										
Chongwe Rural HC	864	99	864	99	0	0	0	0	646	296
Ngwerere rural HC	346	69	346	12	-	-	-	-	131	57
Newlands Clinic	0	0	2807	272	0	0	95	5	22	1
West Africa										

CIRBA	251	7	251	7	-	-	-	-	-	-
Department of Clinical Science, Nigerian Institute of Medical Research	933	102	0	0	709	113	71	9	235	46
USAC	409	10	-	-	-	-	7	-	-	-

Abbreviations: VIA – Visual Inspection with Acetic acid; VIAC – Visual Inspection with Acetic acid and cervicography; VILI – Visual Inspection with Lugol's Iodine; Pap – Papanicolaou test; HPV/DNA – Human Papillomavirus Deoxyribonucleic acid test, WLHIV – Women Living with HIV, HC – Health center; CEPREF – «Centre d'Excellence de Prise en charge des patients du VIH/SIDA»; CNTS – «Centre National de Transfusion Sanguine»; CIRBA – «Centre Intégré de Recherches Biocliniques d'Abidjan»; USAC – «Unité de Soins Ambulatoires et de Conseil»; CHU – «Centre Hospitalier Universitaire»

Table S12. List of sites by region and country

Central Africa	East Africa	West Africa	Southern Africa
Site - ***Country***	Site - ***Country***	Site - ***Country***	Site - ***Country***
Centre Hospitalo-Universitaire de Kamenge (CHUK) – ***Burundi***	Moi Teaching and referral Hospital- ***Kenya***	Centre Intégré de Recherches Biocliniques (CIRBA) *Pédiatrique et Adulte* ***– Cote d'Ivoire***	Lighthouse Trust ***– Malawi***
L'Association Nationale de Soutien aux Seropositifs et maladies du sida (ANSS) - ***Burundi***	Lumumba Hospital ***– Kenya***	Centre National de Transfusion Sanguine (CNTS)***– Cote d'Ivoire***	Rahima Moosa mother and child hospital***– South Africa***
Nyarugunga health centre – ***Rwanda***	Morogoro Regional Hospital – ***Tanzania***	Centre de Prise en charge, de Recherche et de Formation (CEPREF) ***- Cote d'Ivoire***	Newlands clinic ***– Zimbabwe***
Gidondo health centre – ***Rwanda***	Tumbi Special Hospital ***– Tanzania***	Unité de Soins Ambulatoire et de Conseil (USAC) ***- Cote d'Ivoire***	Chongwe health centre ***– Zambia***
Kabuga health centre– ***Rwanda***	Kisesa Health Centre ***– Tanzania***	Centre Hospitalier Universitaire de Sourô Sanou – ***Burkina Faso***	George health centre***– Zambia***
Busanza health centre – ***Rwanda***	Mbarara Regional Hospital ***– Uganda***	Department of Clinical Science, Nigerian Institute of Medical Research, Lagos- ***Nigeria***	Kanyama hospital ***– Zambia***
Masaka health centre– ***Rwanda***	Masaka Regional Hospital ***– Uganda***		Ngwerere health centre ***– Zambia***
	Infectious Diseases Institute ***– Uganda***		Seboche Mission hospital ***– Lesotho***
			Chiure hospital ***– Mozambique***
7 sites	**8 sites**	**6 sites**	**9 sites**

File S1. Good practices identified in sites visited

During our study, we performed sites visits mainly in southern Africa and recorded some good practices across items from screening organization to data reporting. Regarding screening organization and costs, three sites had a dedicated unit for screening with dedicated staff and infrastructure for screening and pre-cancer treatment. This strategy reduced some previously identified barriers to screening including long patient waiting times by eliminating multitasking of staff across units. This also improved patient-provider communication, thus efficiency across the screening pathway. Cervical cancer screening and treatment of pre-cancerous lesions were free of charge in all sites that had treatment services on-site. This improved accessibility of these services to women who were unable to pay for these services. Task shifting was common. In all ten sites visited in SSA, trained nurses performed screening with VIA/VILI and VIAC, and treatment of lesions using cryotherapy or thermal ablation. In one site, the capacity of three laboratory technicians had been enhanced to process slides for pathology. This eased bottlenecks in services delivery mostly linked to high workload on physicians. In southern Africa, two research centres had created unique patient identifiers. One of the centers (Centre for Infectious Disease Epidemiology and Research, Cape Town), assigned each patient a code at ART initiation and attached the printed codes to patient files for subsequent consultations and data collection. The other center (the Western Cape Provincial Health Data Centre, Cape Town) used unique identifiers to link records from the fragmented databases (laboratory, pharmacy, admissions, disease codes, transfers) and infer health conditions.

In two other sites, weekly and monthly reports for CC screening were produced by CC screening staff, and transmitted to the Ministry of Health which allowed for programme monitoring. A few sites had created partnerships with the U.S President's Emergency Plan for AIS Relief (PEPFAR), Ariel Glaser foundation, Agence Nationale de Recherche sur le Sida et les hépatitis virales (ANRS) and the Ruedi Lüthy foundation, who provided some screening infrastructure, contributed to training staff on screening and treatment and supported the development of electronic data systems for data collection and monitoring. Partnerships has been reported by IARC as one of the best practices in cervical screening programmes.

11.4. Supplementary Information Publication 4

Davidović M, Dhokotera T, dos-Santos-Silva I, Bohlius J, Sengayi-Muchengeti M. Breast cancer in women by HIV status: a report from the South African National Concer Registry. PLoS One. 2024 Jun 17;19(6):e0305274.

The supplementary information is available from: https://doi.org/10.1371/journal.pone.0305274, accessed July 14, 2024.

Table of content

Figure S1. Flow chart selection of study cases from the South African National Cancer Registry in study period (2004-2014)

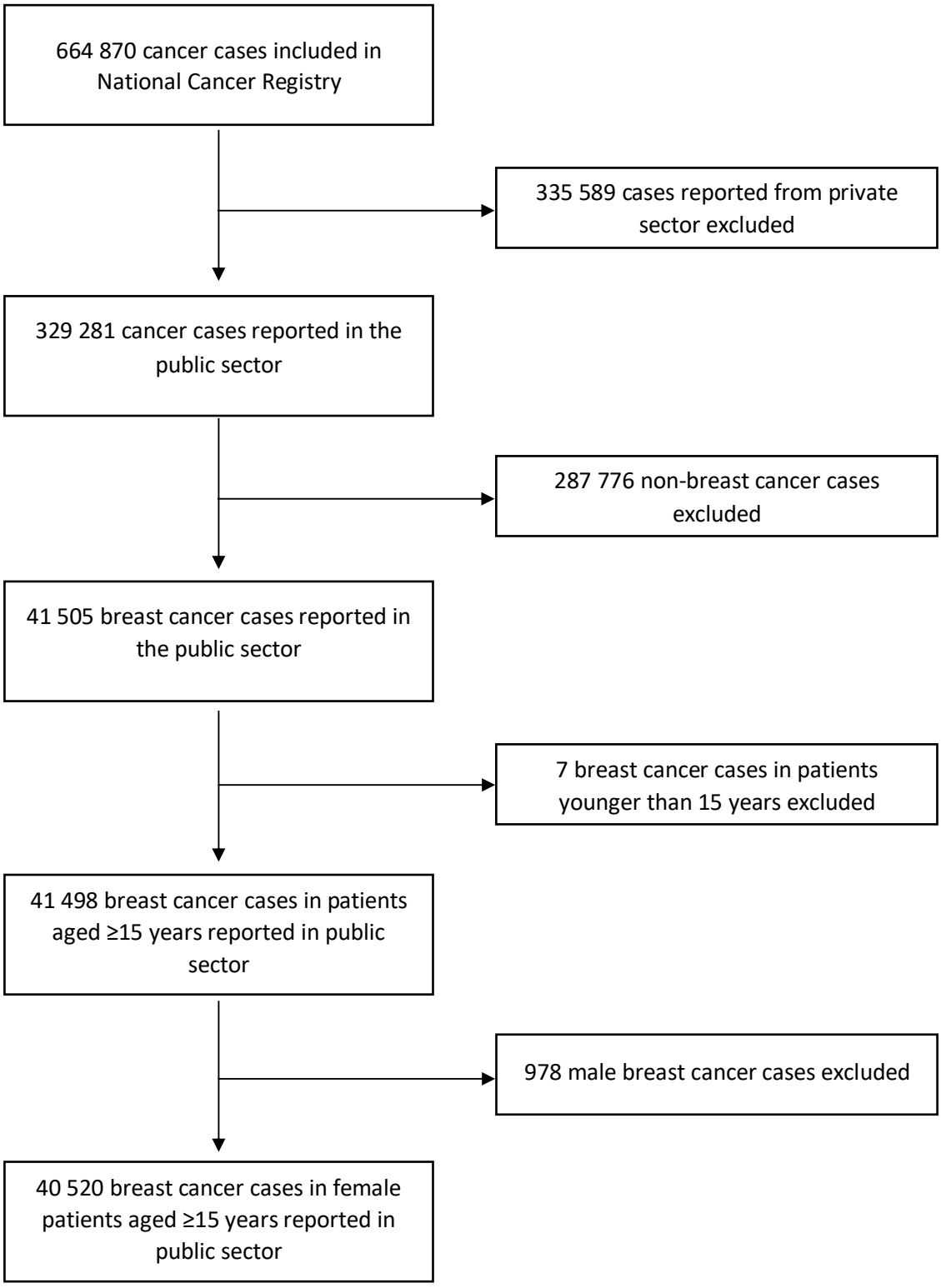

Table S1. Characteristics of female breast cancer patients stratified by HIV status (known, unknown)

	HIV known N (%)	HIV unknown N (%)	Total N (%)	P-value
Patient-level characteristics				
Age at cancer diagnosis [years]				
15-24	56 (0.5)	131 (0.4)	187 (0.5)	
25-29	241 (2.3)	422 (1.5)	663 (1.7)	
30-34	661 (6.2)	1 004 (3.5)	1 665 (4.2)	
35-39	1 107 (10.4)	1 793 (6.2)	2 900 (7.3)	
40-44	1 413 (13.3)	2 772 (9.5)	4 185 (10.5)	
45-49	1 528 (14.3)	3 380 (11.6)	4 908 (12.4)	< 0.001
50-54	1 453 (13.6)	3 460 (11.9)	4 913 (12.4)	
55-59	1 246 (11.7)	3 486 (12)	4 732 (11.9)	
60+	2 961 (27.8)	12 618 (43.4)	15 579 (39.2)	
Missing	60 (n.a.)	728 (n.a.)	788 (n.a.)	
Median age (IQR)	51 (42 – 61)	57 (46 – 68)	55 (45-66)	
Ethnicity				
Asian	216 (2.1)	1 277 (4.5)	1 493 (3.8)	
Black	5 879 (56.4)	17 526 (61.4)	23 405 (60.1)	
Colored	2 212 (21.2)	4 177 (14.6)	6 389 (16.4)	< 0.001
White	2 115 (20.3)	5 554 (19.5)	7 669 (19.7)	
Missing	304 (n.a.)	1 260 (n.a.)	1 564 (n.a.)	
Cancer-level characteristics				
Tumor morphology				
Ductal and Lobular Neoplasms	9 216 (85.9)	25 294 (84.9)	34 510 (85.2)	
Epithelial Neoplasms, NOS	738 (6.9)	2 079 (6.7)	2 817 (6.9)	= 0.01
Adenocarcinomas	291 (2.7)	860 (2.9)	1 151 (2.8)	
Others	481 (4.5)	1 561 (5.2)	2 042 (5.0)	
Year at cancer diagnosis				
2004	184 (1.7)	2 915 (9.8)	3 099 (7.7)	
2005	504 (4.7)	2 794 (9.4)	3 298 (8.1)	
2006	617 (5.8)	2 872 (9.6)	3 489 (8.6)	
2007	683 (6.4)	2 829 (9.5)	3 512 (8.7)	
2008	857 (8.0)	2 886 (9.7)	3 743 (9.2)	
2009	1 030 (9.6)	2 819 (9.5)	3 849 (9.5)	< 0.001
2010	1 117 (10.4)	2 827 (9.5)	3 944 (9.7)	
2011	1 401 (13.1)	2 588 (8.7)	3 989 (9.8)	
2012	1 528 (14.3)	2 776 (9.3)	4 304 (10.6)	
2013	1 466 (13.7)	2 432 (8.2)	3 898 (9.6)	
2014	1 339 (12.5)	2 056 (6.9)	3 395 (8.4)	
Municipality-level characteristics				
Urbanization				
Rural	2 193 (20.7)	8 283 (32.0)	10 476 (28.7)	< 0.001
Urban	8 422 (79.3)	17 606 (68.0)	26 028 (71.3)	

Missing	111 (n.a.)	3 905 (n.a.)	4 016 (n.a.)	
Socio-economic position				
Low	244 (2.3)	1 934 (7.5)	2 178 (6.0)	
Middle	438 (4.1)	2 695 (10.4)	3 133 (8.6)	< 0.001
High	9 932 (93.6)	21 182 (82.1)	31 114 (85.4)	
Missing	112 (n.a.)	3 983 (n.a.)	4 095 (n.a.)	
Province				
Gauteng	3 246 (30.6)	8 429 (32.7)	11 675 (32.1)	
Western Cape	4 176 (39.3)	5 384 (20.9)	9 560 (26.2)	
Eastern Cape	852 (8.0)	3 786 (14.7)	4 638 (12.7)	
Free State	913 (8.6)	1 760 (6.8)	2 673 (7.3)	
Limpopo	335 (3.2)	2 197 (8.5)	2 532 (7.0)	< 0.001
North West	506 (4.8)	1 415 (5.5)	1 921 (5.3)	
Mpumalanga	211 (2.0)	1 229 (4.8)	1 440 (4.0)	
Northern Cape	184 (1.7)	916 (3.6)	1 100 (3.0)	
Kwazulu-Natal	192 (1.8)	695 (2.7)	887 (2.4)	
Missing	111 (n.a.)	3 983 (n.a.)	4 094 (n.a.)	
Total	**10 726 (26.5)**	**29 794 (73.5)**	**40 520**	

Table S2. Univariable and multivariable analysis

Univariable and multivariable analysis for different explanatory variables in HIV positive breast cancer patients compared to HIV negative breast cancer patients

	UNIVARIABLE ANALYSES OR (95% CI)	MULTIVARIABLE ANALYSES OR (95% CI)
Patient-level characteristics		n=10 258
Age at cancer diagnosis [years]		
15-24	0.96 (0.56-1.65)	0.83 (0.46-1.49)
25-29	1.15 (0.87-1.52)	1.12 (0.82-1.52)
30-34	1.41 (1.16-1.71)	1.38 (1.10-1.71)
35-39	Ref.	Ref.
40-44	0.74 (0.64-0.87)	0.79 (0.66-0.94)
45-49	0.50 (0.43-0.59)	0.56 (0.47-0.67)
50-54	0.36 (0.30-0.42)	0.39 (0.33-0.48)
55-59	0.27 (0.23-0.32)	0.33 (0.27-0.40)
60+	0.12 (0.10-0.14)	0.13 (0.11-0.16)
Ethnicity		
Black	7.92 (7.07-8.86)	6.41 (5.68-7.23)
Non-Black	Ref.	Ref.
Year of cancer diagnosis		
2004-2006	Ref.	Ref.
2007-2010	1.13 (0.98-1.29)	1.17 (0.99-1.38)
2011-2014	0.99 (0.87-1.14)	1.25 (1.06-1.46)
Municipality-level characteristics		
Urbanization		
Rural	2.03 (1.84-2.24)	1.59 (1.40-1.82)
Urban	Ref.	Ref.
Socio-economic position		
Low	7.45 (5.61-9.89)	3.46 (2.48-4.82)
Middle	5.64 (4.60-6.91)	2.69 (2.11-3.42)
High	Ref.	Ref.

CI: confidence interval; n – number of observations: OR – odds ratio; Ref. – reference group.

Table S3. Sub-group analysis – univariable and multivariable analysis

Sub-group analysis – univariable and multivariable analysis for different explanatory variables in HIV positive Black breast cancer patients compared to HIV negative Black breast cancer patients

	UNIVARIABLE ANALYSES OR (95% CI)	MULTIVARIABLE ANALYSES OR (95% CI)
Patient-level characteristics		n=5 739
Age at cancer diagnosis [years]		
15-24	0.86 (0.46-1.63)	0.93 (0.49-1.78)
25-29	1.02 (0.72-1.44)	1.07 (0.75-1.51)
30-34	1.32 (1.03-1.68)	1.32 (1.03-1.7)
35-39	Ref.	Ref.
40-44	0.73 (0.60-0.89)	0.73 (0.60-0.90)
45-49	0.57 (0.46-0.69)	0.57 (0.46-0.70)
50-54	0.39 (0.32-0.48)	0.38 (0.30-0.47)
55-59	0.33 (0.26-0.41)	0.33 (0.26-0.42)
60+	0.13 (0.11-0.16)	0.12 (0.10-0.15)
Year of cancer diagnosis		
2004-2006	Ref.	Ref.
2007-2010	1.03 (0.87-1.22)	1.14 (0.95-1.37)
2011-2014	1.20 (1.02-1.41)	1.35 (1.12-1.61)
Municipality-level characteristics		
Residence		
Rural	1.95 (1.72-2.20)	1.62 (1.38-1.89)
Urban	Ref.	Ref.
Socio-economic position		
Low	3.89 (2.89-5.24)	3.05 (2.16-4.31)
Middle	3.25 (2.60-4.05)	2.50 (1.94-3.22)
High	Ref.	Ref.

CI – confidence interval; n – number of observations; OR – odds ratio; Ref. – reference group.

Declaration of Originality

Last name, first name: Davidović, Maša

Matriculation number: 18-133-603

I hereby declare that this thesis represents my original work and that I have used no other sources except as noted by citations.

All data, tables, figures and text citations which have been reproduced from any other source, including the internet, have been explicitly acknowledged as such.

I am aware that in case of non-compliance, the Senate is entitled to withdraw the doctorate degree awarded to me on the basis of the present thesis, in accordance with the "Statut der Universität Bern (Universitätsstatut; UniSt)", Art. 69, of 7 June 2011.

Place, date

Basel, 15.04.2024

Signature