



**Understanding the burden of HIV-related cancers in South Africa's Eastern  
Cape Province: A 2002-2017 retrospective study**

**By**

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# **PREAMBLE**

## **Declaration**

I, Akhona Ncinitwa (NCNAKH001), hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: Akhona Ncinitwa

Date: November 2024

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## **Abstract**

**Background:** The Human Immunodeficiency Virus (HIV)-related cancers in South Africa are a critical public health issue that echoes trends seen across other low-middle income countries (LMICs). These cancers include Kaposi sarcoma, non-Hodgkin's lymphoma, and cervical cancer. Understanding the HIV-related cancer trends and incidence is crucial for achieving improved health outcomes. Therefore, this study aims to understand the HIV-related cancers in the Eastern Cape province of South Africa

**Methods:** This retrospective study used secondary analysis of data generated by the Eastern Cape Cancer Registry linked to the HIV database from the National Health Laboratory Services through probabilistic record linkage to identify and characterise cancer among people living with HIV. Included were cancer cases reported between 1st January 2002 and 31st December 2017 of adult men and women diagnosed with HIV-related cancers. Statistical analysis was done using STATA18.0. A join-point regression model was used to characterise the cancer trends. The Kaplan-Meier curve was used for survival analysis.

**Results:** The sample comprised 1183 eligible cancer patient records, with 1044 (88.3%) females. The HIV prevalence among cancer patients was 74.5%. Specifically, 75.5% of males and 74.3% of females were living with HIV. The trends of Kaposi sarcoma showed an increase between 2002 and 2015 with an annual percentage change (APC) of 17.4%, and between 2015 and 2017, trends decreased with an APC of 22.6%. Cervical cancer trends decreased between 2002 and 2004 with an APC of 14.4%; from 2004 to 2017, there was a sharp increase of 33.2% APC. Kaposi sarcoma had the highest survival median of 3.1 years ( $p=0.06$ ) for people living with HIV, followed by non-Hodgkin's lymphoma with 2.9 years ( $p=0.96$ ), and lastly cervical cancer with 2.5 years ( $p=0.73$ ).

**Conclusion:** The growing burden of cervical cancer and Kaposi sarcoma among people living with HIV remains a problem in the Eastern Cape. Therefore, targeted interventions such as regular screening, early diagnosis, access to appropriate treatment, a system to track treatment adherence and survival rates, appropriate resource allocation, and targeted educational programmes are needed to address the burden.

## List of abbreviations

ADCs	AIDS-defining cancers
AIDS	Acquire immune deficiency syndrome
APC	Annual percentage change
ART	Antiretroviral therapy
ASR	Age-standardised rates
CDC	Centre for disease control and prevention
CDW	Corporate data warehouse
EBV	Epstein Barr virus
ECCR	Eastern Cape Cancer Registry
GLOBOCAN	Global Cancer Observatory
HBV	Hepatitis-B virus
HCV	Hepatitis-C virus
HHV-8	Human herpes virus 8
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
ICC	Invasive cervical cancer
KS	Kaposi sarcoma
KSHV	Kaposi sarcoma-associated herpesvirus
LMICs	Low-middle income countries
NCR	National cancer registry
NHL	non-Hodgkin's lymphoma
NHLS	National health laboratory service
PLWH	People living with HIV
SAMRC	South African Medical Research Council
SDG	Sustainable development goal
STI	Sexually Transmitted Infections
TB	Tuberculosis
WHO	World Health Organisation

## **PART A: PROTOCOL**

## **PROTOCOL SYNOPSIS**

### **Title: Understanding the burden of HIV-related cancers in South Africa's Eastern Cape Province: A 2002-2017 retrospective study**

**Aim:** This study aims to estimate the burden of HIV-related cancers using a population-based cancer register in the Eastern Cape Province during the period from 2002 to 2017

#### **Objectives:**

- Identify and count the number of cancer cases in people living with HIV in the cancer surveillance area for the period 2002-2017.
- To describe the profile of cancer patients in people living with HIV during 2002-2017.
- To estimate trends in cancer patients in people living with HIV for the period 2002-2017.
- To determine cancer survival by HIV status for the period 2002-2017.

#### **Background**

The burden of cancer is increasing in South Africa, like in other developing countries. It is estimated that in Africa, cancer cases increased from 715 000 in 2008 to 1.1 million in 2020, according to the Global Cancer Observatory (1) (2020) (2). The South African National Cancer Registry (NCR) reported 85 373 cases of cancers diagnosed in 2019 (3), and these cases have increased to 108 168, according to GLOBOCAN estimates (4). The World Health Organization (WHO) highlighted that the increase is due to risk factors such as population ageing, unhealthy lifestyles, infectious agents and family history (5). Furthermore, immunodeficiency and coinfections with other oncogenic viruses are risk factors for developing cancer among people living with HIV (PLWH) (6).

The Centers for Disease Control and Prevention (CDC) classified Kaposi sarcoma, cervical cancer and non-Hodgkin's lymphoma (7) as AIDS-defining cancers (ADCs) because of their association with increased risk of human immunodeficiency virus (HIV) infection (8). It is estimated that PLWH are 500 times more likely to be diagnosed with Kaposi sarcoma, 12 times more likely to be diagnosed with non-Hodgkin's lymphoma, and three times more likely to be diagnosed with cervical cancer (9). These ADCs were also noted as one of the most common cancers in South Africa by the NCR (3) and in

the Eastern Cape by the Eastern Cape Cancer Registry (ECCR) (10). Over the years from 2002-2017, the NCR reports have shown inconsistent trends of cervical cancer and non-Hodgkin's lymphoma cases, but there was an increase in the trends of Kaposi sarcoma until 2008 and were inconsistent thereafter (11). Over the same period of years as NCR, the ECCR reported a constant increase in cervical cancer, Kaposi sarcoma and an inconsistent trend of non-Hodgkin's lymphoma (12, 13).

The effective introduction of antiretroviral therapy (ART) in 2004, together with its integration into public hospitals across South Africa, has led to health improvements and enhanced survival rates for PLWH (14). However, before the rollout of ART, PLWH were highly vulnerable to various cancers (8), particularly Kaposi sarcoma, non-Hodgkin's lymphoma, and cervical cancer, due to their compromised immune system (15). As ART became more accessible in the mid-2000s, there was a notable decline in HIV-related cancers (16).

The successful rollout of ART actively reduced the burden of new HIV infections, although it gave rise to non-HIV-related cancers (17) and a significant decrease in the incidence and prevalence of ADCs (8). This study seeks to understand whether the decrease in ADCs will be observed in the population covered by the ECCR. The results of this study will be useful in planning for the health needs of this population and guiding a sound intervention in public health policy.

## **Methods**

### **Study Design**

This is a retrospective study using secondary data generated by the ECCR, which is population-based. A probabilistic record linkage will be used to match cancer records provided by the ECCR to HIV data provided by the National Health Laboratory Service (7). The two information will be linked at the NCR, where HIV status will be added to cases provided by the ECCR. A probabilistic method or model is based on probability theory or the fact that randomness plays a role in predicting future events. This will be achieved by using non-unique keys such as first, last name and date of birth combination to link two pieces of information. To deal with typographical differences, pre-merge data cleaning will be performed on both datasets (ECCR and NHLS).

### **Study population and sampling**

The researcher will apply for permission from the South African Medical Research Council (SAMRC) to access the cancer database. SAMRC is the custodian of ECCR data. Only cancer cases reported by the ECCR between 1<sup>st</sup> January 2002 and 31<sup>st</sup> December 2017 will be retrieved. Cases retrieved from the database will only be adult men and women who were diagnosed with one of the following cancers: cervical, non-Hodgkin's lymphoma (7) and Kaposi Sarcoma. Variables to be explored will include patients' demographic information (name, surname, address, age, sex, and ethnicity), the primary organ invaded by the tumour (topography), histological classification of the cancer tissue (morphology), incidence date (first date the patient was seen by the doctor and cancer diagnosed) and healthcare facility in which the patient was first diagnosed with cancer. After retrieval, this information will be exported to a Microsoft Excel spreadsheet. Only the researcher will work with this information. There will be no direct contact with patients.

### **Data Safety and Monitoring**

Data retrieved will be exported to a password-protected Microsoft Excel spreadsheet and kept on the computer. Only the researcher will have access to this data. After record linkage by NCR, all cases will be given a unique study identifier for confidentiality purposes. All information identifying the cases will be removed.

### **Data Analysis**

Matched cases will be transferred into STATA 17 for analysis. Descriptive data analysis will determine the number of cancer cases identified among PLWH. This will be stratified by age, sex, site, and magisterial area. A logistic regression model will be used to determine the association between cancer and HIV. Survival analysis will be done to determine cancer survival by HIV status using the Kaplan-Meier curve.

### **Ethical Considerations**

Ethical approval will be sought from the University of Cape Town Human Research Ethics Committee (UCT-HREC). Upon receiving approval from UCT-HREC, the study will request approval to access the NHLS database to seek HIV information and permission to access the ECCR database from the SAMRC.

**Risks and Benefits**

Precautionary measures to uphold confidentiality and anonymity will be exercised throughout the study. There is no likelihood of any risks and dangers to the cases used. There is no direct benefit to the cases. However, the results of this study will provide a better understanding of the burden of these cancers for better treatment and management. It is anticipated that future generations will benefit from those resources and reduce mortality due to cancer in this population, which is currently under-resourced. The results of this study will be published to contribute to scientific knowledge.

**Informed consent**

This study will not require informed consent from the participants as they have already consented to the ECCR study.

**Confidentiality**

The Microsoft Excel spreadsheet containing the patient information will be password protected, and only the researcher and the NCR will have access to it for data linkage. After linkage, the information identifying the respondents will be removed, and respondents will be given a unique identification number to maintain confidentiality. Thereafter, only the principal investigator and the researcher will have access to the data.

**Reimbursement for Participation**

This is not applicable as the study does not involve the physical participation of respondents.

**Dissemination of Research Findings**

The proposed study will be submitted as a mini dissertation to meet the requirements of completing a Master of Public Health Degree at the University of Cape Town.

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## **PART B: LITERATURE REVIEW**

## **Introduction**

Human Immunodeficiency Virus (HIV)-related cancers are recognised as a significant public health concern both globally and in regions severely impacted by the HIV epidemic, such as sub-Saharan Africa (1). It is understood that HIV does not directly cause cancer, but over time, it weakens the immune system, thereby increasing the risk of various cancers in People Living with HIV (PLWH) (2). Without effective treatment, HIV infection progresses to Acquired Immunodeficiency Syndrome (AIDS), which in turn leads to AIDS-defining cancers (3). The Center for Disease Control and Prevention (CDC) has classified AIDS-defining cancers as aggressive non-Hodgkin's lymphoma (3), Kaposi sarcoma, and invasive cervical cancer (4). These cancers were among the first reported manifestations of what later came to be identified as AIDS (2), and they tend to occur more often in people whose immune systems have been weakened by HIV or AIDS (5). A deeper understanding of this dual burden will facilitate the development of techniques to enhance the immune response to control HIV and to produce effective cancer treatments in South Africa.

## **Objectives**

- Identify and count the number of cancer cases in people living with HIV in the cancer surveillance area for the period 2002-2017.
- To describe the profile of cancer patients in people living with HIV during 2002-2017.
- To estimate trends in cancer patients in people living with HIV for the period 2002-2017.
- To determine cancer survival by HIV status for the period 2002-2017.

## **Literature search strategy**

Searches for relevant publications were conducted using PubMed, Google Scholar and Google. Search terms used were HIV, AIDS, cancer, malignancies, HIV-related cancers, and AIDS-defining cancers. Additional articles were identified from reference lists and bibliographies of articles extracted by the initial search. The search was restricted to studies conducted in English only. Furthermore, all study designs were considered; however, prospective longitudinal study designs were essential. Studies that could not

be obtained from the databases were excluded; all other studies found were considered for the literature summary.

## **Summary of the literature**

### **Prevalence of HIV-related cancers**

A growing link between HIV and cancer has been noted over the years in both developed and developing countries (6). This link dates back to the first clinical descriptions of a cluster of Kaposi sarcoma cases in 1981, which would eventually be identified as AIDS (7); then, later on, non-Hodgkin's lymphoma and cervical cancer were included in the case definition for AIDS. In the early 1990s, certain viruses were discovered as viruses that worked together with HIV to cause cancer in PLWH (8). These viruses were human papillomavirus (HPV), Human Herpes Virus 8 (HHV-8) (also known as Kaposi sarcoma-associated herpesvirus (KSHV), hepatitis B or C virus (HBV or HCV), or Epstein Barr virus (EBV) (8). Immunodeficiency and co-infections with other oncogenic viruses were also noted as risk factors for developing cancer in PLWH (9).

The high rates of HIV infection in the Eastern Cape province of South Africa have a significant impact on the prevalence of HIV-related malignancies (10). A study of data from more than five million PLWH in South Africa found that cervical cancer was the most common cancer among women, with 7 418 cases reported, followed by Kaposi sarcoma, which had 6 380 cases (11). This trend is consistent across various provinces, including the Eastern Cape. A study conducted by Somdyala et al. (12) found that the Eastern Cape has historically shown a high incidence of cervical cancer, which is worsened by limited access to screening and treatment services. Dhokotera et al. (13) noted that cervical cancer is the second most common cancer and the leading cause of cancer-related deaths amongst women in South Africa, while the Eastern Cape Cancer Registry reported that during the period from 1998 to 2012, cervical cancer was one of the leading cancers among females in the region (14). During the same period, Kaposi sarcoma had a lower incidence than other cancers like lung cancer (14). However, Kaposi sarcoma was the leading cancer among males in a South African HIV cancer match study (15) and in a study in Tanzania (16)

In South Africa, it is estimated that approximately 1 in 176 men and 1 in 265 women will develop non-Hodgkin's lymphoma at some point in their lives (17), making non-Hodgkin's lymphoma to be less prevalent in this region. However, in Korea, cervical cancer and non-Hodgkin's lymphoma were prevalent among women infected with HIV (18). It is, however, acknowledged that the overall incidence of lymphomas is underreported due to challenges in diagnosis and reporting within healthcare facilities in South Africa (14). Although more recent data specifically focusing on the Eastern Cape is limited, national trends suggest that cervical cancer remains a critical concern for women living with HIV in this region (13). This situation could be extrapolated to the Eastern Cape due to the region's high HIV prevalence. Factors such as limited healthcare resources and infrastructure can significantly impact the effectiveness of cancer treatment and prevention approaches, especially for cervical cancer.

Nonetheless, there is a concerning trend of increasing rates of non-AIDS-defining cancers as well, as PLWH in the Eastern Cape age due to improved antiretroviral therapy (ART) (19). While ART has led to a decline in some AIDS-defining cancers like Kaposi sarcoma, the rise of cervical cancer and non-AIDS-defining cancers highlights the need for comprehensive cancer prevention and control strategies.

### **Profile of cancer in people living with HIV**

Cancer in PLWH presents notable demographic, clinical, and behavioural profiles compared to the general population (20). These factors include age, gender, race, healthcare access, treatment response, and lifestyle factors. These differences can influence their health outcomes and the management of both HIV and cancer (21). Studies have shown that PLWH tend to develop cancers at younger ages, usually between 30 and 60 years, compared to older cancer patients without HIV (15, 22). A study in the United States of America (USA) noted the median age of above 50 years, placing them at a growing risk of age-related malignancies that are common in the general population (23, 24). Tanzania noted that the age above 50 years had a higher prevalence of HIV-related cancers despite the use of ART (16). However, in South Africa, the median age is around 40 years for all cancers diagnosed among PLWH (18). This indicates that many individuals are diagnosed at an age when they are still at risk for both HIV-related and non-HIV-related cancers.

Men are more commonly affected by cancers such as Kaposi sarcoma (15, 16, 18, 25), non-Hodgkin's lymphoma (3), and anal cancer, especially men who have sex with men

in regions such as sub-Saharan Africa and countries bordering the Mediterranean sea (8), mainly due to co-infections with oncogenic viruses like HPV (26). However, Semango et al. (27) found that Kaposi sarcoma is more likely to develop in women than men. In women, invasive cervical cancer (ICC) remains one of the most common cancers, especially in regions like sub-Saharan Africa, including South Africa, where HIV is highly prevalent (28, 29). In a South African study by Dhokotera et al. on the association of HIV and cancer, about 50% of females were at higher risk of AIDS-defining cancers (30).

### **Trends of HIV-related cancers**

Different trends in cancer incidence vary by geographical location under study. Studies have demonstrated that advances in ART have significantly reduced AIDS-related morbidity and mortality (8, 31). Before the development of effective ART, ADCs, specifically Kaposi sarcoma and non-Hodgkin's lymphoma, in the USA occurred in 30% or more of patients who had AIDS (8). However, the introduction of combination ART (cART) led to a decrease in the risk of AIDS development, improved immune function and survival, and a decline in incidence rates of ADCs (4, 8). A significant decrease of 70% or more in the incidence of Kaposi sarcoma and non-Hodgkin's lymphoma in developed countries was noted, especially after the introduction of three-drug cART regimens in the mid-1990s, and continued to decrease after 2000 (8). Notably, Kaposi sarcoma has become less common in the USA and continues to decline (25). These declines are linked to expanded HIV care, improved viral suppression, and earlier HIV diagnosis among PLWH (32).

In Sub-Saharan African countries, several studies on HIV-related cancers have been conducted; however, there is no conclusive evidence on how the association has changed in the era of ART (19). However, during periods 2001–2010 and 2011–2016, 11 out of 16 registries with sufficient trend data showed a decline in Kaposi sarcoma incidence (33). In a recent study conducted in South Africa, a decrease in the incidence of Kaposi sarcoma and non-Hodgkin's lymphoma in the ART era was noted; however, cervical cancer remained at an increased rate (34). This decline is linked to a decrease in new HIV infections after the roll-out of ART, which in turn brought about an increase in longevity among PLWH (35). As PLWH age, the trends in the incidence of non-AIDS-defining cancers increase (4, 36). Nonetheless, the incidence of ADCs remains

higher among PLWH compared with HIV-uninfected individuals, even in settings with extensive ART coverage (37). The trends of HIV-related cancers provide insight into the changing landscape of HIV care, oncogenic viruses, and the implications of ageing in this population.

### **Cancer survival among people living with HIV**

Cancer survival estimates vary widely depending on the cancer type, stage at diagnosis, person's health, and the availability of treatment (38, 39). Studies done in developed countries have reported survival rates of five and above years after diagnosis (40, 41), and since the mid-20th century, survival has improved in many cancer sites. One study showed that approximately 16.9 million survived cancer, and this is projected to reach more than 22.1 million by 2030 (39). However, developing countries have shown poor cancer survival rates (42); a study in Malawi displayed a survival median time of about nine months, and only 6% of patients survived for longer than five years (43). Like other developing countries, South Africa showed lower cancer survival rates among PLWH than among HIV-negative individuals, 54% versus 63% (44). McGee-Avila et al. (45) also highlighted that PLWH have worse survival after a cancer diagnosis than people without HIV, partially due to inequities in receipt of cancer treatment. On the other hand, patients who receive cancer treatment have higher survival rates than those who do not (46). Therefore, as life expectancy increases among PLWH diagnosed with cancer, survival estimates are becoming increasingly significant (38). Additionally, PLWH diagnosed with cancer are at a higher risk of dying from that cancer than people without HIV because of compromised immune systems (47).

### **Cervical cancer survival among people living with HIV**

Cervical cancer is a major health concern for South African women living with HIV. It remains a leading cause of cancer-related mortality, particularly among women living with HIV (13). Much has been done for the early detection of cervical cancer in South Africa, like introducing screening services such as Papanicolaou (Pap) smears and HPV vaccination (48). Enhanced access and awareness of these services improved cervical cancer survival rates (49). However, underutilising these services by PLWH often resulted in later-stage disease presentations. This delayed diagnosis negatively affects treatment outcomes and survival rates (49). For instance, a study by Turdo et al. (49) stated that women living with HIV who presented themselves at later stages (six months

of diagnosis) of cervical cancer have greater mortality rates than HIV-negative individuals. It was further observed that as the years progressed, the proportion of survival rates among PLWH decreased compared to those without HIV(49). The WHO recommended that women living with HIV should be screened for cervical cancer at the time of their HIV diagnosis and then every three years thereafter, provided that the initial screening test is negative (50). This approach aims to facilitate early detection and intervention, thereby improving cervical cancer survival rates in PLWH.

### **Kaposi sarcoma survival among people living with HIV**

Kaposi sarcoma can lead to severe problems and possibly life-threatening conditions if left untreated (51), especially in individuals with a compromised immune system due to HIV infection. However, to enhance the immune system of PLWH, the initiation of ART plays a crucial role (52). Immune system suppression is associated with a reduction of Kaposi sarcoma incidence rate and elongated survival rates (53).

The rollout of ART in South Africa started in 2004 (54). This initiative aimed to improve health outcomes for PLWH, including those with opportunistic infections (54, 55). Likewise, this approach brought about change for patients with Kaposi sarcoma, a cancer often associated with advanced HIV infection (55). Literature showed that in South Africa, mortality rates for Kaposi sarcoma patients were lower by 63% during the late ART period (2009–2012) compared to the early ART period (2004–2008) (55). Apart from introducing ART, the South African government expanded ART eligibility and increased access to treatment by introducing the test-and-treat strategy in 2016 (54). This earlier initiation of ART correlated with lower Kaposi sarcoma incidence rates (55) and has altered the epidemiology of HIV-associated malignancies (56). For example, patients who initiated HIV care during the post-expansion period compared to earlier periods had a lower risk of developing Kaposi sarcoma (56). However, some patients do not respond to ART as expected and, at times, present with advanced Kaposi sarcoma at diagnosis (55). In such instances, alternative treatment such as chemotherapy or radiation therapy may become necessary (51). The combination of these treatments was found to yield better survival results for Kaposi sarcoma. However, in South Africa, more needs to be done as Kaposi sarcoma incidence in PLWH remains unacceptably high, even in patients on ART, and this may have negative effects on Kaposi sarcoma mortality.

### **Non-Hodgkin's lymphoma survival among people living with HIV**

In southern African countries, non-Hodgkin's lymphoma has been identified as a high-burden disease, largely attributed to the HIV epidemic (57), with 12.3% of mortality rates associated with this condition (58). In South Africa non-Hodgkin's lymphoma is not one of the leading causes of mortality among PLWH; however, if not monitored and treated, it can cause sudden death (59). However, the survival rate for individuals diagnosed with non-Hodgkin's lymphoma differs depending on a range of risk factors. Among these risks, age at diagnosis plays a significant role, particularly when the onset occurs in individuals aged 60 years or older (60), especially in the ART era. Before the roll-out of ART, patients with AIDS-related lymphomas were poorly diagnosed and had a median survival time ranging from five to eight months (61). Research indicates that older patients often face more complex health challenges and may have a poorer prognosis compared to younger patients (62). In addition, factors such as gender (specifically males), treatment completion, and low socioeconomic status have been associated with poor survival outcomes in patients with non-Hodgkin's lymphoma (62).

### **Conclusion**

In conclusion, HIV-related malignancies are a substantial public health concern, especially in high-HIV-prevalence areas such as South Africa's Eastern Cape. While ART has lowered the prevalence of HIV-related cancer, such as Kaposi sarcoma, cervical cancer remains a major concern, particularly among women living with HIV. Co-infections with other viruses and immunodeficiency are major factors driving this trend. As PLWH ages, because of improved ART, non-AIDS-defining malignancies are becoming more common. Developing countries have problems in cancer detection and treatment, resulting in lower results for PLWH with cancer. A better understanding of HIV-related cancer epidemiology is critical for strengthening prevention and control methods. However, more data is required to accurately quantify the burden in places such as South Africa. Therefore, it is valuable to understand the burden of HIV-related cancers in the Eastern Cape province of South Africa.

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## **PART C: MANUSCRIPT**

**Title of the article**

Understanding the burden of HIV-related cancers in South Africa's Eastern Cape Province: A 2002-2017 retrospective study

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As per the UCT MPH dissertation guidelines, supervisors are not to be listed as authors in the journal-ready manuscript but instead have their contribution to the finished work mentioned in the acknowledgements.

## **Abstract**

**Background:** In South Africa, Human Immunodeficiency Virus (HIV)-related cancers are a critical public health issue whose prevalence trends are seen across other low to middle-income countries. These cancers include Kaposi sarcoma, non-Hodgkin's lymphoma, and cervical cancer. Understanding these HIV-related cancer trends and incidence is crucial for achieving improved health outcomes. Therefore, this study sought to investigate HIV-related cancers in the Eastern Cape province.

**Methods:** This retrospective study used secondary analysis of data generated by the Eastern Cape Cancer Registry linked to the HIV database from the National Health Laboratory Services through probabilistic record linkage to identify and characterise cancer patients living with HIV. Included were cancer cases reported between 1st January 2002 and 31st December 2017 of adult men and women diagnosed with HIV-related cancers. Statistical analysis was done using STATA18.0. A join-point regression model characterised the cancer trends and Kaplan-Meier curve for survival analysis.

**Results:** The sample comprised 1183 eligible cancer patients, with 1044 (88.3%) females. The HIV prevalence among cancer patients was 74.5%. Specifically, 75.5% of males and 74.3% of females were living with HIV. The trends of Kaposi sarcoma showed an increase between 2002 and 2015 with an annual percentage change (APC) of 17.4%, and between 2015 and 2017, trends decreased with an APC of 22.6%. Cervical cancer trends decreased between 2002 and 2004 with an APC of 14.39%; from 2004 to 2017, there was a sharp increase of 33.19% APC. Kaposi sarcoma had the highest survival median of 3.1 years ( $p=0.06$ ) for people living with HIV, followed by non-Hodgkin's lymphoma with 2.9 years ( $p=0.96$ ), and lastly cervical cancer with 2.5 years ( $p=0.731$ ).

**Conclusion:** The growing burden of cervical cancer and Kaposi sarcoma among people living with HIV remains a problem in the study setting. Therefore, targeted interventions such as regular screening, early diagnosis, access to appropriate treatment, and a system to track treatment adherence and survival rates are needed. Moreover, appropriate resource allocation and targeted educational programmes are needed to address this burden.

## **Introduction**

The Human Immunodeficiency Virus (HIV) pandemic continues to be recognised as a significant global public health issue (1). Although trends in HIV have shifted over time, both progress and ongoing challenges remain evident in various countries (2). Over the years, the global HIV prevalence has shown a steady increase of 5.4 million between the early 2000s to 2010 and by five million between 2010 and early 2023 (3). According to the World Health Organization (WHO), it is estimated that there are 39.0 million people living with HIV (PLWH) globally (3). African countries account for a substantial proportion of this increase, with approximately two-thirds (25.6 million) of PLWH residing in the region (3). Furthermore, several African countries have reported an increase in new infections despite previously experiencing declines (3). In sub-Saharan Africa, for example, women and girls represented 63% of all new HIV infections in 2022 (4). In South Africa, the HIV prevalence rate is estimated to be 13.9% (5), translating to approximately 8.45 million PLWH in 2022 (6). Despite the rising prevalence, the number of new HIV infections both globally and in South Africa has demonstrated a steady decline, attributed mainly to the implementation of various interventions and strategies (5, 6). These interventional approaches include the 95-95-95 strategy, early detection and prevention measures, health promotion education, and expanded access to antiretroviral therapy (ART) (7, 8).

Research has indicated that ART extends the life expectancy of PLWH (9), though it also increases the risk of developing other health complications, such as cancer, tuberculosis (TB), and severe diarrhoea (10). It is estimated that approximately 20% of all deaths among PLWH are attributable to cancer, which has emerged as an increasing public health challenge (11). The global incidence of cancer has been rising steadily and is expected to continue doing so (12). According to the WHO, cancer is the second leading cause of death worldwide (13). Global Cancer Observatory (14) estimated that there were 20 million newly diagnosed cancer cases globally in 2022, with 9.7 million deaths (13). Of these cancer cases, 1.2 million (5.9%) were reported in African countries. In South Africa, as in other African nations, the cancer burden, alongside cancer-related mortalities, is projected to escalate in the coming years (15). The incidence of cancer in South Africa was approximately 110 000, with more than 56 000 cancer-related deaths in 2020, representing a quarter of premature non-communicable disease-related mortality (15). Nevertheless, several cancer control strategies have been

implemented to address the growing cancer burden (7) in line with efforts to ensure healthy lives and promote well-being for all ages (Sustainable Development Goal 3 (SDG-3)) (16).

However, the burden of HIV-related cancers has become a growing concern despite the existence of strategies aimed at addressing both HIV and cancer. This is due to the compromised immune system caused by HIV, which makes it more challenging to detect and eliminate cancer cells (17). Cancers commonly associated with HIV include Kaposi sarcoma, non-Hodgkin's lymphoma, and cervical cancer (18). This burden of HIV-related cancers is particularly pronounced in low- and middle-income countries (LMICs), where HIV prevalence is high (4) and access to healthcare remains limited. Additionally, PLWH often present with advanced stages of cancer, exacerbating the strain on already overstretched healthcare systems, particularly in African regions (17).

In South Africa, HIV-related cancers are a critical public health issue, mirroring trends observed in other LMICs (19). A comprehensive understanding of HIV-related cancer trends and incidence is essential for improving health outcomes, advancing public health goals, and addressing SDG-3. Studies (19-21) investigating the burden of HIV-related cancers in South Africa have predominantly focused on urban areas, highlighting the need for further research in rural parts of the country. This study, therefore, aimed to understand the burden of HIV-related cancers in the Eastern Cape province of South Africa.

## **Methodology**

### **Study Setting**

This study was conducted as a secondary analysis of data collected in a prospective cancer cohort study of cases registered by the Eastern Cape Cancer Registry (ECCR) in the Eastern Cape Province of South Africa, a predominantly rural area. According to the national population census (2022), the Eastern Cape is home to over 7.2 million people, representing 12% of South Africa's population, and covers an area of 168 966 km<sup>2</sup> (22). The ECCR covers parts of three districts of the Eastern Cape province, namely the Alfred-Nzo, OR Tambo and Amathole districts, out of six district municipalities. From these district municipalities, the ECCR covers four subdistricts,

which include Winnie Madikizela-Mandela (WMM), Ngquza Hill, Mnquma and Mbashe. Out of these subdistricts, nine magisterial areas were selected, which included eight rural areas: Bizana, Flagstaff, and Lusikisiki in the North-Eastern region; Butterworth, Centane, Nqamakwe, Idutywa and Willowvale in the South-Western region, and one urban area, Buffalo City, in the East Coast region. These subdistricts differ in geographical location, infrastructure, and access to healthcare services; WMM is known as the poorest subdistrict compared to others. The eight rural magisterial areas for this study were selected based on complete data availability from 2002 to 2017.

### **Study design and data linkage**

This retrospective study utilised secondary analysis of data generated by the ECCR, which was linked to the HIV database from the National Health Laboratory Services (23) (23) through probabilistic record linkage. This process was employed to identify and characterise cancer patients who were living with HIV. The variables examined included patients' demographic information (name, surname, address, age, sex, and ethnicity). Additional demographic characteristics were the primary organ affected by the tumour (topography), the histological classification of the cancer tissue (morphology), the incidence date (the first date the patient was seen by a doctor and the cancer was diagnosed), and the healthcare facility where the cancer was initially diagnosed. The data accessed from the database were stored in an encrypted spreadsheet on a password-protected computer to maintain confidentiality.

### **Data sources**

#### **Cancer registry for cancer data**

The ECCR is a population-based cancer registry that was established in 1998 by the South African Medical Research Council (SAMRC) to provide comprehensive, accurate, and timely data on cancer incidence and distribution (24). This information is intended to support and inform cancer control and prevention programmes. The ECCR uses standardised data collection forms from nine magisterial areas (urban and rural) of the Eastern Cape to collect data. A detailed description of the ECCR operations is explained elsewhere (24, 25).

## **National Health Laboratory Services for HIV data**

The NHLS is a national public entity established in 2000 (23). The NHLS mandate is to ensure the provision of quality, affordable, and sustainable health laboratory services, as well as training and research. Laboratories have been established in all nine provinces of South Africa, with pathology services being provided to over 80% of the South African population.

### **Data linkage**

Before linkage, the data were cleaned to remove duplicates, and the districts from which the patients originated were added. The linkage of the cancer cases with the HIV cases was carried out using a probabilistic matching algorithm, utilising the Corporate Data Warehouse (CDW) of the National Cancer Registry (NCR) (15). The software is designed to ensure that all laboratory records belonging to the same individual are linked within the entire NHLS database (21). The variables used for linkage included name, surname, date of birth, identity number, and district. The record linkage was conducted independently of the HIV and cancer data in collaboration with an NCR researcher. Records deemed a match were those with a matching probability of 90% or higher.

### **Study population and sampling**

Cancer cases reported by the ECCR between 1st January 2002 and 31st December 2017 were included in the study. The study focused on adult men diagnosed with non-Hodgkin's lymphoma and Kaposi sarcoma, as well as women diagnosed with cervical cancer, non-Hodgkin's lymphoma, and Kaposi sarcoma. Only cases from the eight rural magisterial areas were considered for the study. In contrast, those from one urban magisterial area were excluded, as this area had only been included in the surveillance from 2015. Children under the age of 18 years and cases of non-HIV-related cancers were also excluded. Of the 3 630 linked cancer cases, duplicate cases were removed. A total of 3 114 cancer cases were found to match, while 516 cases did not and were subsequently excluded from the analysis. From the matching cases, 1 931 were excluded due to unknown HIV status, leaving 1 183 cases with known HIV status, which were used for analysis.

## **Data Analysis**

Statistical analysis was conducted using Stata statistical software version 18.0 (STATA Corp, College Station, Texas, USA). The median and interquartile range (75th percentile – 25th percentile) were employed to summarise the participants' ages in years. The Wilcoxon sum rank test was utilised to compare the equality of median ages. Categories were compared using Fisher's exact test when the expected frequencies were less than five. In cases where the p-value was not specified in Tables 1 and 2, a Chi-square test was applied. A join-point regression model (Join-Point Regression Program, Version 5.2.0) was used to characterise the trends in cancer rates over time and to determine the magnitude of the change (Annual Percentage Change (APC)) for selected cancers. The line graphs were fitted in Join-point using Age Standardised Rates (ASRs) (dots). The Kaplan-Meier curve was employed for survival analysis to estimate survival outcomes for the data from 2002 to 2017. Model diagnostics were performed using Cox-Snell, Deviance, and Schoenfeld residuals.

## **Ethical Approval**

The ECCR received approval from the Human Research Ethics Committee of the SAMRC (EC014: 10/2014). The current study was approved by the Ethics Committee of the Faculty of Health Sciences, University of Cape Town (HREC: 760/2022).

## **Results**

### **Description**

Among the 1 183 eligible cancer patients from the ECCR database that were successfully linked with the NHLS HIV database, 1 044 (88.3%) were identified as female. The population was found to be almost racially homogenous, with 99.9% (n=1 182) classified as black African. The HIV prevalence among these eligible cancer patients was recorded at 74.5% (n=881) (Table 1). Specifically, 75.5% (n=105) of males and 74.3% (n=776) of females were identified as living with HIV. Over half of the cohort (57.5% or n=681/1 183) was reported to be unemployed.

The median age at cancer diagnosis for the entire cohort was 43 years (75th percentile = 55 years and 25th percentile = 35 years), corresponding to an age range of 35 to 55 years.

It is further indicated in Table 1 that a higher HIV prevalence was observed among cancer survivors in the younger age group (18-29 years), while the cancer prevalence among HIV-negative individuals was found to increase with increasing age, being 7.7% (n=9/302) for those aged 18-29 years and 65.3% (n=62/302) for those above the age of 70 years.

As such, age, marital status, district, sub-district and occupation revealed statistically significant differences ( $p < 0.0001$ ) in HIV prevalences among cancer survivors. The detailed sociodemographic characteristics are summarised in Table 1.

**Table 1: Socio-demographic characteristics of people living with HIV and HIV-negative individuals with cancer (2002-2017)**

Characteristics		Total		PLWH		HIV negative		p-value
<b>Sample; n (%)</b>		1183	(100.0)	881	(74.5)	302	(25.5)	<0.0001 <sup>s</sup>
<b>Sex; n (%)</b>								
	Male	139	(100.0)	105	(75.5)	34	(24.5)	0.759
	Female	1044	(100.0)	776	(74.3)	268	(25.7)	
<b>Age, years; med (IQR)</b>		43	(20)	40	(15)	56	(22)	<0.0001 <sup>r</sup>
<b>Age, years; n (%)</b>								
	18-29	117	(100.0)	108	(92.3)	9	(7.7)	<0.0001
	30-39	338	(100.0)	302	(89.3)	36	(10.7)	
	40-49	315	(100.0)	255	(81.0)	60	(19.0)	
	50-69	318	(100.0)	183	(57.5)	135	(42.5)	
	>70	95	(100.0)	33	(34.7)	62	(65.3)	
<b>Ethnicity; n (%)</b>								
	African	1182	(100.0)	881	(74.5)	301	(25.5)	0.255 <sup>#</sup>

	White	1	(100.0)	0	(0)	1	(100.0)	
<b>Marital status; n (%)</b>								
	Single	281	(100.0)	248	(88.3)	33	(11.7)	<0.0001 <sup>#</sup>
	Married	548	(100.0)	392	(71.5)	156	(28.5)	
	Widow	19	(100.0)	8	(42.1)	11	(57.9)	
	Divorced	3	(100.0)	2	(66.7)	1	(33.3)	
	Unknown	332	(100.0)	231	(69.6)	101	(30.4)	
<b>District; n (%)</b>								
	OR Tambo	657	(100.0)	495	(75.3)	162	(24.7)	<0.0001
	Alfred Nzo	254	(100.0)	213	(83.9)	41	(16.1)	
	Amathole	272	(100.0)	173	(63.6)	99	(36.4)	
<b>Subdistrict; n (%)</b>								
	Ingquza Hill	657	(100.0)	495	(75.3)	162	(24.7)	<0.0001
	WMM	254	(100.0)	213	(83.9)	41	(16.1)	
	Mnquma	154	(100.0)	107	(69.5)	47	(30.5)	
	Mbashe	118	(100.0)	66	(55.9)	52	(44.1)	
<b>Occupation; n (%)</b>								
	Unemployed	681	(100.0)	502	(73.7)	179	(26.3)	<0.0001
	Employed	107	(100.0)	99	(92.5)	8	(7.5)	
	Not stated	395	(100.0)	280	(70.9)	115	(29.1)	
<sup>S</sup> Two-sample test of proportions used; WMM=Winnie Madikizela-Mandela; <sup>#</sup> Fisher's Exact test used; <sup>¶</sup> Wilcoxon rank sum test used; If the p-value is not specified, then the Chi-squared test was used								

Table 2 presents cancer trends among PLWH and HIV-negative cases and the associated survival probabilities. It was observed that between 2005-2009 and 2010-2017, the proportion of PLWH decreased from 89.2% to 72.3%, while the proportion of HIV-negative individuals increased from 10.8% to 27.7%. The highest proportion of cancer cases was recorded among PLWH ( $p < 0.05$ ). Additionally, a high proportion of cases were cytologically verified (85.1%) among PLWH in comparison to those verified clinically (76.0%) and histologically (72.3%). Among the treatment options, surgery, radiation therapy and chemotherapy, patients with comorbid cancer and HIV most had radiation therapy (20.2%, 178/881), followed by chemotherapy (13.2%, 116/881), then surgery (2.5%, 22/881). Further noted in Table 2 is that alternative treatment was received by 85.1% (748/879) of patients with comorbid cancer and HIV. Survival probabilities for patients living with cancer are shown in Table 2, Figures 1 and 2 and stratified by HIV status. Whilst not statistically significant, the overall survival median was 2.5 years for the entire period, 2.6 years for PLWH and 2.5 years for HIV-negative patients (Table 2). Kaposi sarcoma had the highest survival median of 3.1 years ( $p=0.06$ ) for PLWH, followed by non-Hodgkin's lymphoma with 2.9 years ( $p=0.96$ ), and lastly cervical cancer with 2.5 years ( $p=0.73$ ).

**Table 2: HIV-related cancer trends, treatment and survival in people living with HIV and negative individuals, 2002-2017.**

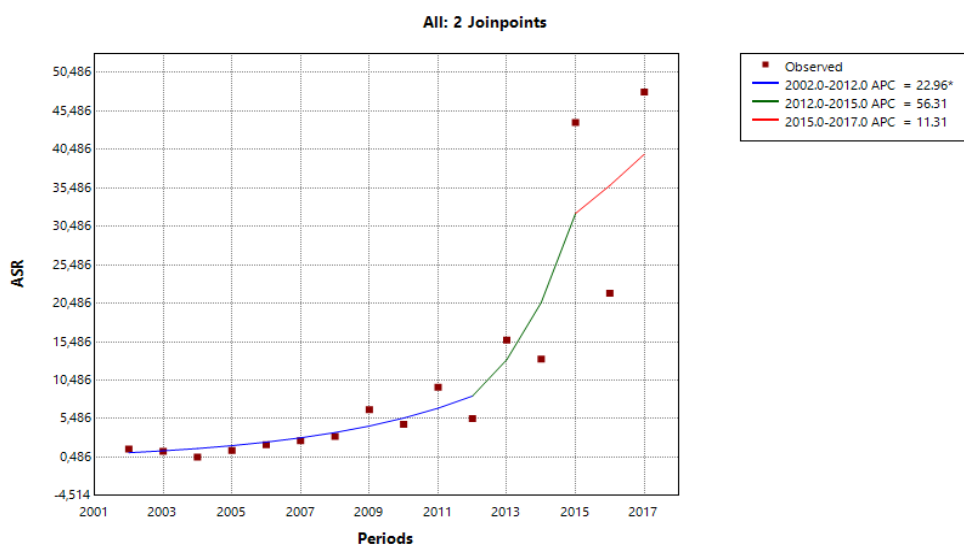
Characteristics		Total		PLWH		HIV negative		p-value
<b>Year of HIV diagnosis; n (%)</b>								
	2002-2004	25	(100.0)	20	(80.0)	5	(20)	<0.0001
	2005-2009	139	(100.0)	124	(89.2)	15	(10.8)	
	2010-2017	1019	(100.0)	737	(72.3)	282	(27.7)	
<b>Cancer; n (%)</b>								
	Cervix	898	(100.0)	646	(71.9)	252	(28.1)	0.001 <sup>#</sup>
	Kaposi sarcoma	266	(100.0)	221	(83.1)	45	(16.9)	
	Non-Hodgkin's Lymphoma	19	(100.0)	14	(73.7)	5	(26.3)	
<b>Basis of diagnosis; n (%)</b>								

	Clinical	121	(100.0)	92	(76.0)	29	(24.0)	0.002
	Cytology	168	(100.0)	143	(85.1)	25	(14.9)	
	Histology	894	(100.0)	646	(72.3)	248	(27.7)	
<b>Surgery; n (%)</b>								
	Yes	29	(100.0)	22	(75.9)	7	(24.1)	0.862
	No	1154	(100.0)	859	(74.4)	295	(25.6)	
<b>Radiation; n (%)</b>								
	Yes	279	(100.0)	178	(63.8)	101	(36.2)	<0.0001
	No	904	(100.0)	703	(77.8)	201	(22.2)	
<b>Chemotherapy; n (%)</b>								
	Yes	168	(100.0)	116	(69.0)	52	(31.0)	0.082
	No	1015	(100.0)	765	(75.4)	250	(24.6)	
<b>Alternative treatment; n (%)<sup>b</sup></b>								
	Yes	991	(100.0)	748	(75.5)	243	(24.5)	0.059
	No	190	(100.0)	131	(68.9)	59	(31.1)	
<b>Stage; n (%)<sup>a</sup></b>								
	1	20	(100.0)	15	(75.0)	5	(25.0)	0.420
	2	94	(100.0)	56	(59.6)	38	(40.4)	
	3	203	(100.0)	138	(68.0)	65	(32.0)	
	4	63	(100.0)	42	(66.7)	21	(33.3)	
<b>Survival duration, years; med (IQR)</b>								
	Cervix	2.5	(4.3)	2.5	(4.6)	2.5	(3.5)	0.731
	Kaposi sarcoma	3.0	(5.0)	3.1	(5.7)	2.3	(3.8)	0.055

	Non-Hodgkin's Lymphoma	3.4	(5.5)	2.9	(5.9)	3.4	(2.9)	0.963
	Total	2.5	(4.6)	2.6	(4.7)	2.5	(3.7)	0.602
<b>Status</b>								
	Deceased	414	(100.0)	276	(66.7)	138	(33.3)	<0.0001
	Alive	769	(100.0)	605	(78.7)	164	(21.3)	
<b>NHL=Non-Hodgkin's Lymphoma; #Fisher's Exact test used; <sup>β</sup>n=1181/1183 (99.8%); <sup>α</sup>n=380/1183 (32.1%); If the p-value is not specified, then the Chi-squared test was used</b>								

Table 2 also depicts that two-thirds (66.7%, 276/414) of the individuals who had died were PLWH.

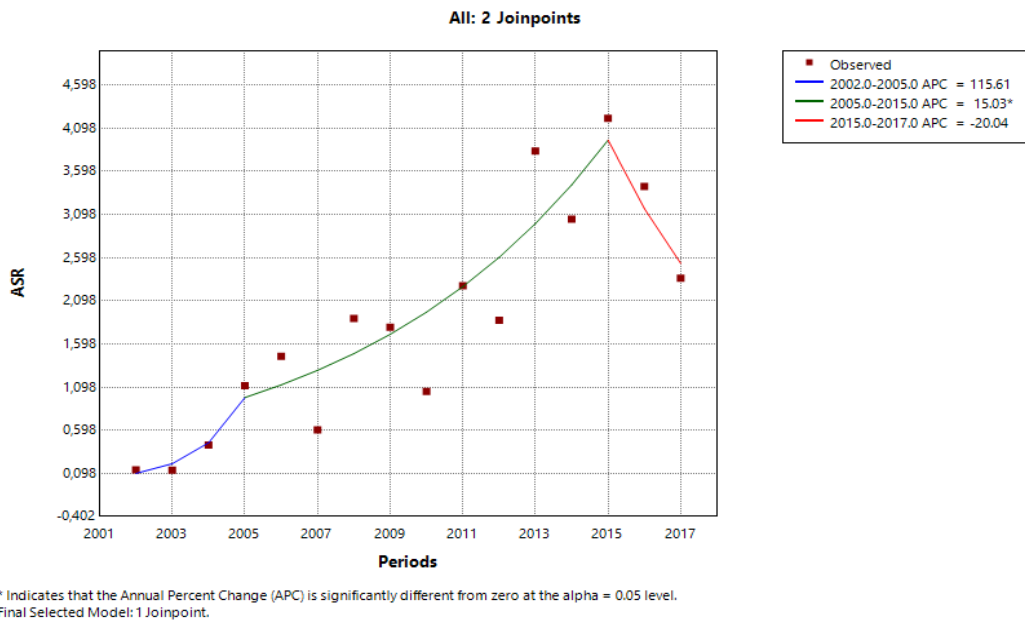
Figure 1 depicts a Joinpoint analysis to identify points where a significant change in the trend of cervical cancer occurs. From 2002 to 2004, the APC is -14.39. This indicates a decrease in ASR during these years. From 2004 to 2017, the APC is 33.19, showing a significant increase in the ASR during these years, with the APC change showing a statistically significant change at  $p < 0.05$ . The trends show that after 2004, there was a sharp increase in the ASR, indicating a growing trend in the prevalence of cervical cancer.



\* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.  
Final Selected Model: 0 Joinpoints.

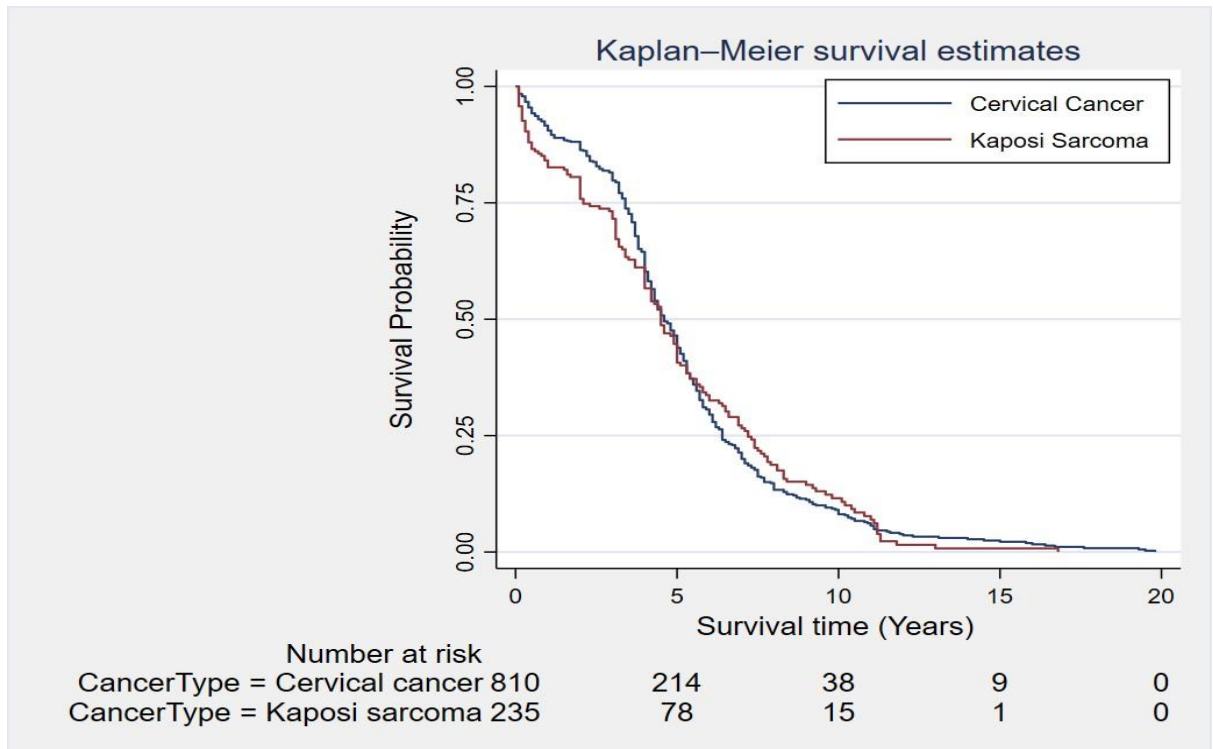
**Figure 1: Joinpoint regression model showing the Annual Percentage Change (APC) of cervical cancer trends, 2002-2017.**

Figure 2 depicts the trend of ASRs of Kaposi sarcoma over time from 2002 to 2017. The period from 2002 to 2015 depicts an increase in trends of Kaposi sarcoma, with an APC of 17.4%. This indicates that the change is statistically significant,  $p < 0.05$ . However, from year 2015 to 2017, a decrease in trends, with an APC of 22.6%, is shown.



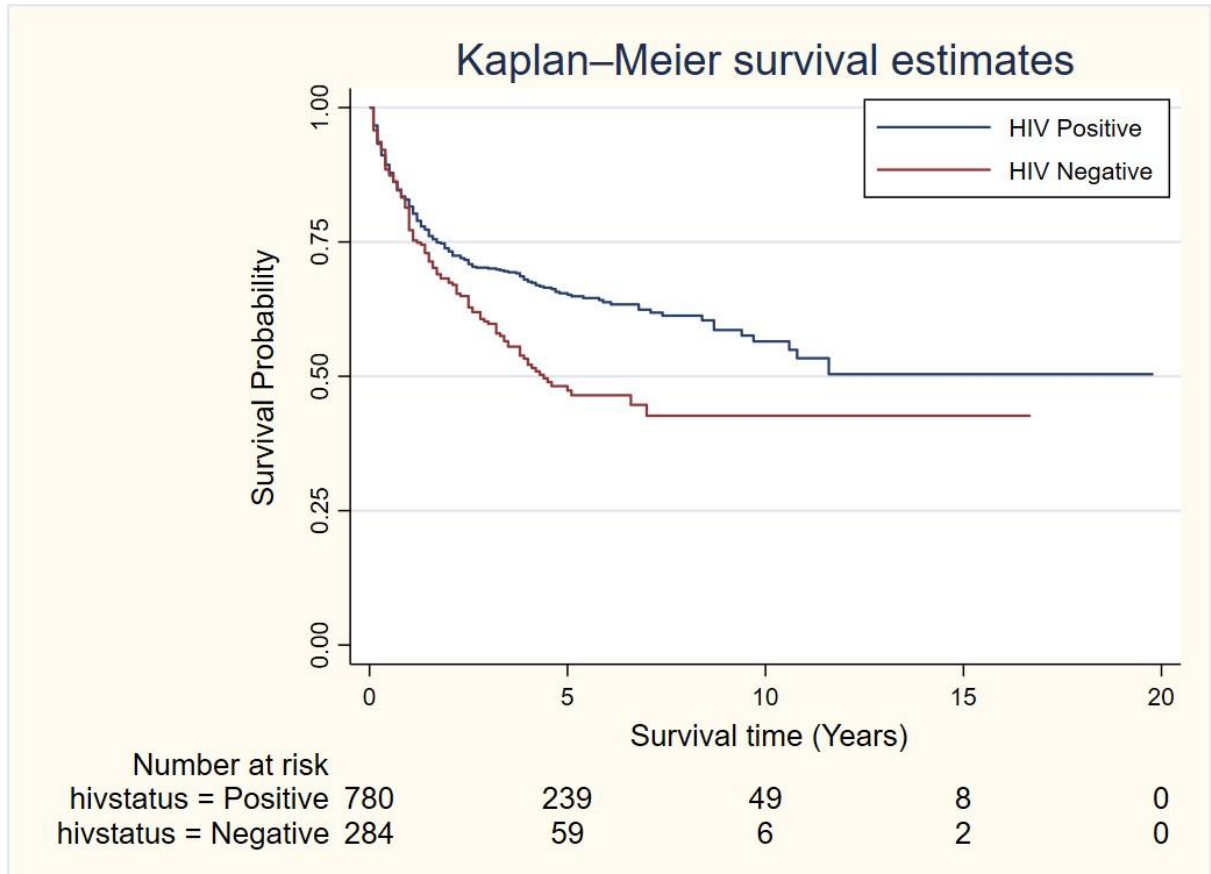
**Figure 2: Join-point regression model showing Annual Percentage Change (APC) of Kaposi sarcoma trends, 2002-2017.**

Figure 3 indicates that the probability of survival for Kaposi Sarcoma survivors after 2.5 years is approximately 75%, and 85% for cervical cancer. However, after four years, for both cancers, the survival probability is approximately 55%.



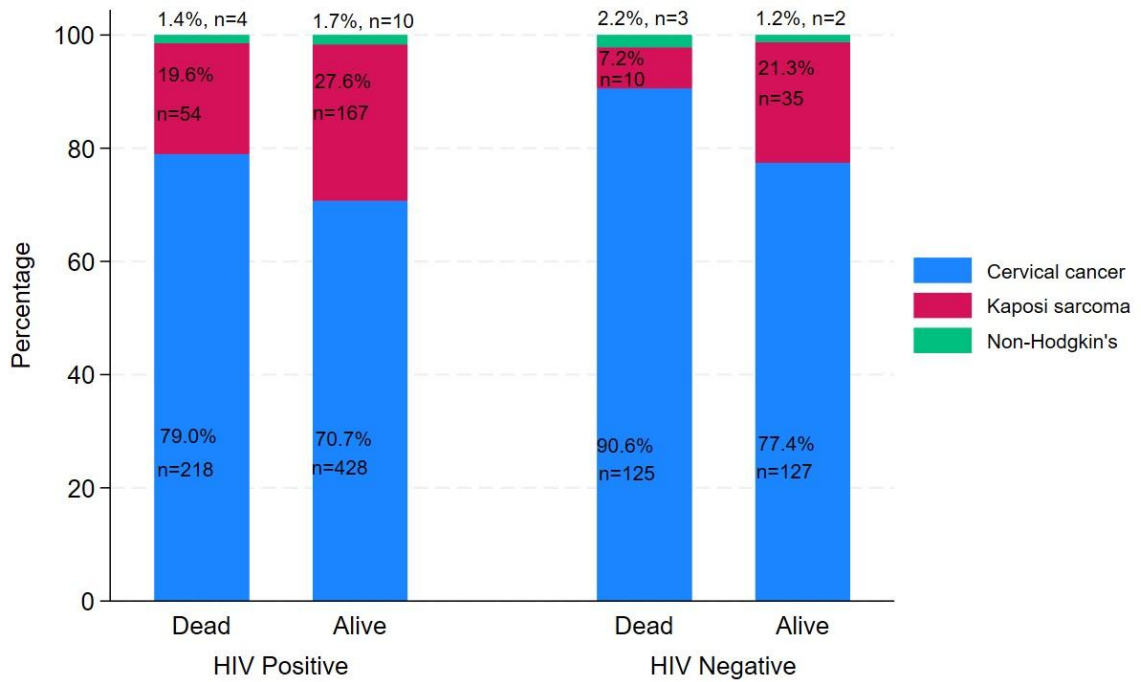
***Figure 3: Kaplan-Meier survival estimates for survival probability of cervical and Kaposi sarcoma cancer in PLWH, 2002-2017.***

Figure 4 shows that at year one, the survival probability for HIV-negative patients is approximately 78% and 80% for PLWH. However, in year five, the graph shows a good survival probability for PLWH of approximately 65%.



***Figure 4: Kaplan-Meier survival estimates of HIV-related cancers in people living with HIV and negative individuals, 2002-2017.***

Figure 5 shows the vital status stratified by cancer type and HIV status. Despite the HIV status, individuals are most likely to die from cervical cancer, with 79.0% in PLWH and 90.6% in HIV-negative individuals, compared to individuals with Kaposi sarcoma and non-Hodgkin’s lymphoma.



**Figure 5: Percentage of vital status stratified by cancer type in PLWH and negative individuals, 2002-2017**

### Discussion

This retrospective study of 16 years aimed at understanding HIV-related cancers in the Eastern Cape province through the triangulation of cancer and HIV databases. The population was comprised mainly of unemployed individuals. Statistically significant differences were found in HIV prevalence among cancer survivors when patients' records were assessed by age, marital status, district, sub-district, and occupation. Furthermore, a statistically significant association was noted between different cancer types in PLWH and HIV-negative individuals, as well as the diagnostic modalities, if the treatment option was radiation therapy and the survival outcomes.

The fact that prevalence of HIV-related cancers varied by age group; among PLWH, higher HIV prevalence is observed in younger people under 20 years of age (26) and in older individuals aged 30 to 45 years (27, 28). In comparison, HIV-negative individuals are detected in older individuals aged 60 years and above (29). In this study, cancer prevalence was inversely correlated with age among individuals who were HIV-negative and highest in younger age groups among PLWH. This notion was supported by a previous South African study, which reported that PLWH get some cancers at a

younger age than the general population (7). A London-based research also found that adolescents and young adults with perinatally acquired HIV had a median age of 19 years at cancer diagnosis, which is significantly younger than the average cancer diagnosis in the general population (30). The findings from this study emphasise that the younger PLWH are at high risk of early-onset cancer. Therefore, to address this issue, age-specific intervention programmes, such as the National Youth HIV Prevention Strategy, the Determined, Resilient, Empowered, AIDS-free, Mentored and Safe (DREAMS) initiative, the Peer Education initiative, and Pre-exposure Prophylaxis (PrEP) targeting the youth, should be strengthened.

Among individuals with cancer in this study, the HIV prevalence was highest among single individuals across different marital statuses. These findings are consistent with a Ugandan study, which also found that marriage reduces HIV transmission (31). Similarly, it was found in a Cameroonian study that women with cervical cancer who were single or divorced were more likely to be living with HIV than those who were married (32), due to unstable exclusive relations. In contrast, a South African study found that married individuals had a higher prevalence of HIV compared to unmarried individuals (33). On the other hand, Shisana et al. reported that married couples living apart are more prone to HIV infections than those living together (34). Therefore, these contrasting views suggest that marital status as a predictor of HIV among cancer patients would need to be studied within the context of that specific population rather than merely concluding.

The highest HIV prevalence among individuals with cancer was noted in the Alfred Nzo district in this study, which is the poorest district in the country (35), and this could be attributed to barriers such as health inequity and difficulties in accessing healthcare (36). Willie and Maqbool noted distance and transportation as a barrier to accessing health facilities (37). Results from this study highlight the need for better treatment and prevention programs, proper resource allocation, and increased access to HIV testing and cancer screening for early detection and treatment.

This study found that cervical cancer and Kaposi sarcoma were the two cancers most frequently diagnosed among PLWH, while non-Hodgkin's lymphoma had a lower prevalence. In contrast, a study conducted elsewhere in South Africa among adolescents and young adults previously noted Kaposi sarcoma and non-Hodgkin's lymphoma as

the most frequently diagnosed cancers (7). A Kenyan study, on the other hand, indicated that cervical cancer and non-Hodgkin's lymphoma were the most prevalent ADCs (38). In justification of a low prevalence of non-Hodgkin's lymphoma, a study conducted in the United States of America (USA) between 2009 and 2014 highlighted that non-Hodgkin's lymphoma, which was once in PLWH, has now been diminished by ART (39). It was revealed in another study that lymphomas are often misdiagnosed as TB in PLWH in South Africa (20). However, limited screening options cannot be ruled out as potential reasons for the underscreening or underdiagnosis of non-Hodgkin's lymphoma cases (40), unlike cervical cancer, for which various screening options are available.

According to studies, it has been found that women who are living with HIV are considerably more likely to have a high risk of HPV compared to women who are HIV-negative (29, 41, 42). The trends of cervical cancer in PLWH show a significant decrease in the ASR with an APC of -14.39% from 2002 to 2004, followed by a significant increase in the ASR with an APC of 33.19% from 2004 to 2017 in this study. The theory behind the decrease in this study setting could be attributed to factors such as mortality or cervical cancer screening, as well as improved treatment of precancerous cervical lesions (43). The increasing trend after 2004 could indicate that interventions such as increased access to cervical cancer screening, treatment and prevention programs are effective. However, this may also be linked to the fact that cervical cancer is the most prevalent and commonly diagnosed cancer in women (44), and most guidelines recommend screening for cervical cancer (45). Moreover, the effectiveness of the HPV vaccine in young girls, aimed at reducing the risk of developing cervical cancer later in life, needs to be assessed in this region.

Kaposi sarcoma is mainly linked to human herpes virus 8 (HHV-8) reactivation. The results of this study have indicated that a significant majority (83.1%) of Kaposi sarcoma cases occurred in PLWH. This study showed a steady increase in Kaposi sarcoma trends from 2002 to 2015; however, a decrease was observed from 2015 to 2017, with an APC of 22.62%. This decrease is depicted as a trend observed in South Africa following the scaling up of access to ART as part of the National Strategic Plan on HIV, Sexually Transmitted Infections (STIs), and TB (46). The guidelines for ART eligibility were broadened to include earlier treatment initiation, allowing for starting

ART regardless of CD4 count by 2016. The results from our study are supported by a survey conducted in the same setting, which noted a dramatic increase in the incidence of Kaposi sarcoma in both males and females between 1998 and 2012 (25). However, with the introduction of ART, a significant decline in Kaposi sarcoma incidence has been noted in developed western countries, unlike in sub-Saharan countries, where it has become the most common cancer (47). This decline is also observed in this study.

It was displayed in this study that a cancer diagnosis among PLWH is more likely to be based on clinical presentation rather than diagnostic tests and that histological diagnosis is more prevalent among these individuals. This may potentially be attributed to a more advanced disease at presentation. This finding is supported by a study conducted in Uganda, where it was shown that nearly 80% of all patients presented at an advanced stage and that 37% were found to have HIV infection (48). However, it was confirmed by a study performed in Botswana that patients who perceived their symptoms as serious were more likely to be present at the early stages (49). Unfortunately, it has been noted that the late stage of presentation worsens cancer survival among PLWH compared with HIV-negative individuals because treatment completion is less likely to occur (50). Although differences in survival continue to be observed even when the cancer stage at diagnosis is factored in, the diagnosis of cancer at a later stage leads to more difficult treatment procedures and poorer survival outcomes.

Concerning treatment interventions, it is illustrated by this study that individuals, whether living with HIV or HIV-negative, were more likely to receive radiation therapy than chemotherapy or surgical treatment. The surgical intervention was found to be balanced between PLWH and HIV-negative individuals. At the same time, radiation therapy was noted to have potential barriers to care for PLWH, and chemotherapy was commonly used in this population by PLWH. This might be attributed to the fact that PLWH often presented with more advanced stages of localised cervical cancer when surgery is no longer recommended (50).

The results from this study show that in the earlier years, a slightly better early survival rate was observed for cervical cancer compared to Kaposi sarcoma. However, as time progresses, both cancers tend to have similar survival rates. It is advised that the

utilisation of age-appropriate cancer screening may improve outcomes for PLWH (51), as it would lead to a decrease in cancer-associated mortality.

It was observed in this study that higher mortality rates were found in PLWH compared to HIV-negative individuals, with a significant difference of 66.7% and 33.3%, respectively. It was determined by an analysis cohort study that ADCs were the leading cause of death among PLWH (52). Regular screening, early diagnosis, and access to appropriate treatment are considered critical for improving cancer outcomes in this high-risk population.

### **Limitations**

The study faced significant limitations, particularly due to inadequate HIV information, as the ECCR rarely collects comprehensive HIV data, and the NHLS only has records for laboratory-tested cancer patients. This situation raises concerns about the potential underreporting of HIV status among participants. Furthermore, the findings may not be generalisable to other regions with different healthcare systems, economic conditions, or cultural factors that impact the relationship between HIV and cancer. Key issues included limited screening options and the possibility of misdiagnosis, where non-Hodgkin's lymphoma cases might be confused with TB. Additionally, the research did not explore the causes or factors associated with early or late cancer-stage diagnosis presentation in PLWH, further limiting its applicability and depth of analysis. The study also lacked the population-based denominator, which could lead to an inaccurate measure of the true impact of health events within this population.

### **Strengths**

The 16-year retrospective study on HIV-related cancers has revealed an increasing prevalence of these malignancies, alongside advances in HIV treatment and prevention. A comprehensive picture of the HIV-cancer association has been provided by merging data from the NHLS and cancer registries. The importance of integrated healthcare programmes addressing both HIV and cancer management is emphasised, as these can assist in identifying specific demographics or risk factors for targeted public health interventions. Healthcare policymakers and practitioners are expected to benefit from these findings by improving screening, prevention, and treatment efforts for HIV-related cancers. Lastly, collaboration across

healthcare stakeholders that will bring a holistic approach to patient care is encouraged to enhance health outcomes.

### **Conclusion**

In conclusion, HIV prevalence in this study is shown to vary by demographic factors, particularly age, marital status, and geographic location, highlighting the need for targeted interventions to address disparities. The growing burden of cervical cancer and Kaposi sarcoma among PLWH continues to be a concern in this field of study. The study's findings will be used to assess current interventions to monitor the impact of screening uptake and adherence among PLWH. Nevertheless, the ongoing need for monitoring cancer screening in PLWH is emphasised alongside integrated care approaches that incorporate both cancer treatment and HIV management. Sustainable intervention measures such as resource allocation, a system to track treatment adherence and survival rates, and educational programmes on HIV-related cancers must be established to improve patient outcomes.

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## **PART D: APPENDICES**



UNIVERSITY OF CAPE TOWN  
Faculty of Health Sciences  
Human Research Ethics Committee



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28 November 2022

**HREC REF: 760/2022**

**Prof L Myer**

Division of Epidemiology & Biostatistics  
Falmouth Building  
Email: [Landon.myer@uct.ac.za](mailto:Landon.myer@uct.ac.za)  
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Dear Prof Myer

**PROJECT TITLE: THE BURDEN OF HIV-RELATED CANCERS IN THE EASTERN CAPE PROVINCE IS NOT KNOWN; A RETROSPECTIVE STUDY USING A POPULATION-BASED CANCER REGISTRY DATABASE DURING THE PERIOD FROM 2002-2017  
MASTER'S CANDIDATE-MISS AKHONA NCINITWA**

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

**Approval is granted for one year until the 30 November 2023.**

Please submit a progress form, using the standardised Annual Report Form (FHS016) if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: [www.health.uct.ac.za/fhs/research/humanethics/forms](http://www.health.uct.ac.za/fhs/research/humanethics/forms))

***The HREC acknowledge that the student: Miss Akhona Ncinitwa will also be involved in this study.***

**Please quote the HREC REF 760/2022 in all your correspondence.**

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

**PROFESSOR M BLOCKMAN**  
**CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE**

HREC/ref 760.2022

## **Confirmation of language editing**

### **Confirmation of Language Editing**

This letter serves to confirm that I Nongiwe Linette Mhlanga, has provided professional editing services for the manuscript titled “Understanding the Burden of HIV-related Cancers in South Africa’s Eastern Cape Province: A 2002-2017 Retrospective Study” by Akhona Ncinitwa

I have carefully reviewed the manuscript for grammar, punctuation, syntax, and overall clarity. The editing work did not include checking/verifying the information that formed the manuscript, nor did it include improving the structure and flow of the manuscript.

**Yours Faithfully**

**Dr. Nongiwe Linette Mhlanga**