PREVALENCE OF HIV ASSOCIATED CANCER AMONGST INDIVIDUALS OF AFRICAN DESCENT

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PREFACE

This study represents original work by the author and has not been submitted in any other form to any other University. Where use was made of the work of others, it has been duly acknowledged in the text.

The research described in this dissertation was conducted in the Department of Medical Microbiology, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa, under the supervision of Professor Veron Ramsuran.

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DECLARATION

I, JOYCE ADIDJA (225067175), declare that:

The research reported in this thesis, except where otherwise indicated, is my original work.

This thesis has not been submitted for any degree or examination at another university.

This thesis does not contain other persons' data, pictures, graphs, or other information, unless specifically acknowledged as being sourced from other persons.

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SIGNED:  DATE: _____18 February 2026

DEDICATION

To my angel in heaven, my beloved grandmother, Mamy Julienne Mwarabu Onunga.

Thank you for always believing in me, for your endless love, and for being my constant source of motivation and faith.

Though you are no longer here, your wisdom, guidance, love, and unwavering faith continue to live through me every day.

With all my love,

JOYCE A.

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I give thanks to God, who writes straight on crooked lines. Your grace, wisdom, and faithfulness have guided every step of this journey. Through every challenge and unexpected turn, you have shown that your plans are always greater than mine.

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This work is dedicated to advancing knowledge and improving health outcomes for those most in need, with the hope that it contributes to a future of greater equity and compassion.

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2. Joyce Adidja and Veron Ramsuran. The Dual Burden of AIDS-Defining and Non-AIDS-Defining Cancers in People Living with HIV in Sub-Saharan Africa.

PRESENTATIONS

Joyce Adidja (2025), prevalence of HIV associated cancer amongst individuals of African descent. College of Health Sciences Research Symposium, University of Kwa-Zulu Natal, Durban, South Africa – Winner for the 2nd Prize/Poster.

Table of Contents

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

ADC	AIDS Defining Cancer
ART	Antiretroviral Therapy
BREC	Biomedical Research Ethics Committee
CD4+	Cluster of Differentiation 4
CI	Confidence Interval
EBV	Epstein-Barr Virus
HHV-8	Human Herpesvirus 8
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
IALCH	Inkosi Albert Luthuli Central Hospital
KS	Kaposi Sarcoma
KSHV	Kaposi's Sarcoma Associated Herpesvirus
KZN	KwaZulu-Natal
NADC	Non-AIDS Defining Cancer
NHL	Non-Hodgkin Lymphoma
OR	Odds Ratio
PLWH	People Living with HIV
PSA	Prostate Specific Antigen
SCCA	Squamous Cell Carcinoma of the Anus
TNBC	Triple Negative Breast Cancer

ABSTRACT

Background: In sub-Saharan Africa, HIV and cancer represent a critical syndemic; however, detailed epidemiological data amongst individuals who have both conditions remain limited. The widespread rollout of antiretroviral therapy (ART) has shifted the cancer profile among people living with HIV (PLWH) from AIDS -defining cancers to non -AIDS -defining cancers. Yet, the dual burden of HIV and cancer in high-prevalence regions, such as KwaZulu-Natal (KZN), South Africa, is not well characterised. This study attempts to understand this gap in knowledge by (i) estimating the prevalence of HIV infection among cancer patients in KZN; (ii) describing the demographic profile of HIV-positive cancer patients; and (iii) identifying cancer types most strongly associated with HIV status.

Methods and Materials: A nested cross-sectional study was conducted using clinical data from 1,541 adult cancer patients of African descent enrolled in an ongoing Cancer Genetics Study at a tertiary hospital in Durban, KZN, between June 2024 and June 2025. Various clinical demographic characteristics, such as HIV status, ART status, and cancer diagnosis, were extracted. Descriptive statistics and logistic regression models were used to assess associations between HIV and cancer.

Results: The overall prevalence of HIV among cancer patients was 34.8% compared to the national average of 17.2%. All HIV-positive individuals were receiving ART at the time of cancer diagnosis. HIV prevalence was notably higher among female patients (41.2%), Black African individuals (44.7%), and those aged 39–48 years (59.6%). AIDS-defining cancers (ADCs) accounted for 55.4% of all malignancies, while non-AIDS-defining cancers (NADCs) comprised 29.1%. Among specific cancer types, the highest HIV prevalence was observed in vulval cancer (93.2%), anal cancer (72.2%), and cervical cancer (57.1%). Univariable logistic regression analysis revealed significantly increased odds of HIV infection among patients with vulval cancer (odds ratio (OR) 25.97; 95% confidence interval (CI) 7.21–127.40; $p<0.001$), anal cancer (OR 4.94; 95% CI 1.43–19.32; $p=0.0148$), and cervical cancer (OR 2.53; 95% CI 1.16–5.84; $p=0.0224$). A significant negative association was observed for leukaemia (OR 0.28; 95% CI 0.12–0.69; $p=0.0042$), while breast cancer showed no significant association (OR 1.08; 95% CI 0.50–2.48; $p=0.8566$).

Conclusion: This study demonstrates a high prevalence of HIV among cancer-positive patients in KwaZulu-Natal, with varied correlation between HIV and certain cancer types, particularly Human Papillomavirus (HPV)-related malignancies, despite universal ART coverage. The

distinct epidemiological profile supports the need for integrated public health strategies, including targeted cancer screening and HPV vaccination within HIV care programmes.

CHAPTER I: INTRODUCTION

1. Background and the context of the study

More than four decades since its discovery, the human immunodeficiency virus (HIV) continues to pose a significant global public health challenge. As of 2025, an estimated 40.8 million people globally were living with HIV (1). Sub-Saharan Africa accounts for nearly two-thirds of all people living with HIV (PLWH) (2) and faces a growing cancer burden, with approximately 28.7% of cancers attributable to infections (3). South Africa is burdened by a dual epidemic, with an estimated 7.8 million people living with HIV (4) and a significant national cancer burden of over 111,321 new cases and 64,547 cancer-related deaths recorded in 2022 (5). South Africa's cancer profile is significantly shaped by its high HIV prevalence. Infection-related cancers, including Kaposi sarcoma (4,119 new cases) and cervical cancer (10,532 new cases, the third most common cancer nationally), are particularly prevalent (5). KwaZulu-Natal is one of the most severely affected provinces, with an adult HIV prevalence of 16.0% in 2022 (6).

The global rollout of antiretroviral therapy (ART) has fundamentally changed the trajectory of the HIV epidemic, transforming a once fatal infection into a manageable chronic condition (7, 8). This therapeutic success has led to a steadily ageing population of people living with HIV, who now face a new spectrum of health challenges, particularly non-communicable diseases such as cancer. Consequently, cancer has emerged as one of the leading causes of morbidity and mortality among people living with HIV (9). HIV-associated cancers are broadly categorised into two groups: AIDS-defining cancers (ADCs), which include Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), and invasive cervical cancer, and which signal progression to AIDS; and non-AIDS-defining cancers (NADCs), which occur more frequently in people living with HIV than in the general population (10, 11). Despite this research, there is limited information about African populations. The development of these cancers is multifactorial, driven by immunosuppression, chronic inflammation, co-infection with oncogenic viruses (HPV, EBV, and HHV-8), and the direct oncogenic effects of HIV proteins (11-13).

Despite the high prevalence of both HIV and cancer in KwaZulu-Natal, the intersection of these conditions within the local oncology population remains underreported. National studies, such as the South African HIV Cancer Match Study (14, 15), provide valuable broad insights but often lack the site-specific detail required to inform clinical decision-making and resource

allocation at the provincial or hospital level. A significant epidemiological gap persists regarding the co-occurrence of HIV and cancer in KwaZulu-Natal (KZN). The exact prevalence of HIV among cancer patients, along with the profile of HIV-associated malignancies in the province, remains poorly defined. The lack of localised data limits the ability to develop targeted public health strategies, affecting tailored screening, integrated care, and resource allocation. Without such evidence, healthcare planning relies on extrapolated data that do not accurately reflect the unique characteristics of KwaZulu-Natal's dual disease burden.

Addressing this gap is essential for several reasons. First, it establishes baseline data needed to quantify the magnitude of the problem. Second, identifying the cancers most strongly associated with HIV at the local level enables the prioritisation of screening and prevention efforts, such as intensified cervical cancer screening for women or anal cancer screening for high-risk groups. Third, understanding the demographic and clinical profiles of affected patients can inform patient education and counselling strategies. Ultimately, the findings from this study are critical for advocating and designing integrated HIV-oncology services in KwaZulu-Natal to reduce cancer-related disparities and improve survival outcomes for people living with HIV.

The relationship between HIV and cancer is well-established yet continues to evolve in response to changing treatment landscapes. In the pre-antiretroviral therapy (ART) era, AIDS-defining cancers (ADCs) dominated the cancer profile of people living with HIV. The introduction of ART resulted in a marked decline in the incidence of Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL); however, the risk for these and other virus-associated cancers remains substantially higher among people living with HIV compared to the HIV-negative population (15, 16). Notably, the era of effective ART has seen a steady rise in the incidence of non-AIDS-defining cancers (NADCs), including lung, liver, anal, and prostate cancers, which now account for over half of all cancers in some cohorts of people living with HIV (17, 18).

The increased cancer risk in people living with HIV is associated with several biological mechanisms. HIV-induced depletion of CD4+ T cells compromises immune surveillance, allowing the uncontrolled proliferation of infected cells. Additionally, chronic immune activation and inflammation persist even in virologically suppressed individuals, promoting a pro-tumour microenvironment enriched with cytokines that facilitate cellular proliferation, angiogenesis, and metastasis (11-13). HIV proteins, including *Tat* and *Nef*, directly contribute

to oncogenesis by disrupting cell cycle regulation, inhibiting apoptosis, and inducing genomic instability (19).

Globally, HIV-associated cancers are disproportionately concentrated in Africa, which accounts for the largest share of cases. In 2022, over 70% of HIV-attributable cancer cases occurred in Africa, primarily focused in eastern and southern regions, where HIV accounts for more than 10% of all cancers. Southern Africa recorded the highest age-standardised incidence rate worldwide (27.6 per 100,000), compared with just 0.2 per 100,000 in Asia. Within Africa, cervical cancer accounts for approximately 41% of HIV-associated cancer cases, followed by Kaposi sarcoma at nearly 35% (20).

For instance, 64% of women diagnosed with cervical cancer in southern Africa are living with HIV (21). In 2020, HIV significantly contributed to the burden of squamous cell carcinoma of the anus (SCCA) in Africa. Globally, 21% of male SCCA cases occurred among people living with HIV, with the majority concentrated in Africa, North America, and Europe. HIV prevalence among men with SCCA exceeded 40% in 22 countries, predominantly in Africa, underscoring the substantial role of HIV in anal cancer risk across the continent. Among women, 3% of SCCA cases occurred in people living with HIV, primarily in Africa (22). These disparities are driven by high underlying HIV prevalence, high rates of oncogenic viral co-infections, and systemic barriers to healthcare access, including cancer screening and prevention services (23, 24).

A key gap in the literature is the absence of comprehensive data from high-HIV-burden settings such as KwaZulu-Natal. While studies from Johannesburg (25) and national databases offer valuable insights, KZN's distinct demographic and healthcare context necessitates a dedicated investigation. Focused research in KZN is critical to capture the specific profile of HIV-associated malignancies in this unique provincial setting, which may differ due to local risk factors, healthcare access patterns, and genetic diversity. Generating this localised evidence is a necessary step toward effective, tailored interventions.

2. Problem statement

Although KwaZulu-Natal has a high burden of both HIV and cancer, there is a lack of contemporary data describing how these conditions intersect within the local oncology population. This gap is compounded by the evolving cancer profile among people living with HIV, regional disparities in healthcare access, and the absence of evidence-based local guidelines. Key knowledge gaps include the prevalence of HIV among cancer patients in

KwaZulu-Natal, the distribution of cancer types by HIV status, and the demographic and clinical characteristics of HIV-positive cancer diagnoses. Addressing these gaps is critical to reducing the impact of HIV-associated malignancies and informing the development of integrated, evidence-based public health interventions tailored to KwaZulu-Natal's population.

3. Aim

To determine if there is a disproportionate burden of HIV within cancer-positive individuals and determine if there is an association with specific cancer types among oncology patients of African descent in KwaZulu-Natal.

4. Research question

What is the prevalence of HIV infection among cancer patients enrolled in the Cancer Genetics Study at Inkosi Albert Luthuli Central Hospital?

5. Objectives

1) To estimate the overall prevalence of HIV infection within the Cancer Genetics Study cohort.
2) To describe the socio-demographic profile (age, gender, race) of cancer patients and compare these characteristics by HIV status.
3) To assess the distribution of cancer types (ADCs and NADCs) and identify those significantly associated with HIV infection.

6. Hypotheses

a. HIV prevalence among cancer patients is higher than in the general adult population in KwaZulu-Natal.
b. Cancers with a known viral aetiology (e.g., cervical, anal, Kaposi sarcoma) are positively associated with HIV infection.

7. Description of the study area and general methodology

This study was conducted at Inkosi Albert Luthuli Central Hospital (IALCH), a tertiary academic referral hospital in Durban, KwaZulu-Natal. The hospital serves as a primary oncology referral centre for the province. This study utilised existing data from the Cancer Genetics Study, an ongoing research initiative enrolling patients with histologically confirmed cancer for genetic and epidemiological analysis.

A nested cross-sectional design was employed. The study population included all adult (≥18 years) cancer patients of African descent enrolled in the Cancer Genetics Study between June 2024 and June 2025, who were permanent residents of KwaZulu-Natal. Data on demographic characteristics, HIV status, ART status, and cancer diagnosis were extracted from the study database. A consecutive sampling approach was applied, including all eligible participants within the defined study period.

Statistical analyses were conducted using R software. Descriptive statistics were calculated to summarise the study population. Bivariate analyses, including Chi-square tests and independent t-tests, were used to compare groups based on HIV status. Univariate logistic regression models were applied to identify factors associated with HIV infection and specific cancer types. All models were adjusted for potential confounders, including age, gender, and race. Ethical approval for the study was obtained from the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal (protocol number BREC/00008300/2025).

CHAPTER 2

The Dual Burden of AIDS-Defining and Non-AIDS-Defining Cancers in People Living with HIV in Sub-Saharan Africa

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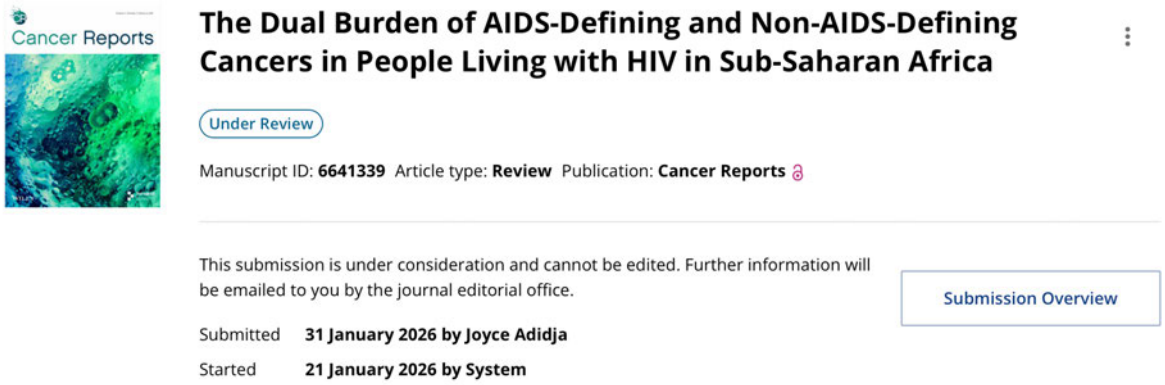

ABSTRACT

Background: The successful scale-up of combination antiretroviral therapy (ART) has transformed HIV into a chronic condition, resulting in an ageing population of people living with HIV (PLWH) who face an increased risk of malignancies. Sub-Saharan Africa (SSA), the global epicentre of the HIV epidemic, now contends with a dual burden of AIDS-defining cancers (ADCs) and a rising incidence of non-AIDS-defining cancers (NADCs).

Methods: This narrative review synthesises evidence published between January 2014 and November 2025. A systematic search was conducted across PubMed, Scopus, Web of Science, and ScienceDirect, supplemented by reports from WHO, UNAIDS, and IARC. Thematic analysis was used to integrate epidemiological, clinical, and molecular data on HIV-associated cancers in SSA.

Results: ADCs such as Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer remain highly prevalent in SSA. This is driven by the high endemicity of oncogenic viruses, including HHV-8, EBV, and HPV, alongside persistent barriers to early HIV diagnosis and care. At the same time, NADCs, including breast, prostate, and anal cancers, are emerging as major causes of morbidity and mortality as the PLWH population ages. Cancers in PLWH in SSA are often characterised by aggressive histology, advanced stage at diagnosis, and poorer survival outcomes. These patterns reflect a complex interplay of HIV-induced immunosuppression, chronic inflammation, co-infections, and significant health system limitations.

Conclusions: Addressing the growing cancer burden among PLWH in SSA requires integration of cancer services within existing HIV programmes. Future strategies should prioritise feasible screening and prevention protocols, supported by a research agenda focused on the region's unique viral, host genetic, and environmental cofactors, to achieve equitable cancer control.

Keywords

HIV, sub-Saharan Africa, AIDS-defining cancers, non-AIDS-defining cancers, cancer disparities, Kaposi sarcoma, breast cancer, prostate cancer, anal cancer

1. Introduction

The introduction of combination antiretroviral therapy (ART) has transformed HIV from a fatal illness into a manageable chronic condition, significantly improving both survival and quality of life among people living with HIV (1, 2). As PLWH live longer, they face an increased risk of ageing-related conditions, particularly malignancies (3). Advanced HIV disease (AHD), a stage of severe immunosuppression, carries a well-documented susceptibility to opportunistic infections and a significantly elevated risk of cancer (4). People living with HIV experience higher rates of several malignancies compared to the general population, drawing increasing attention to the intersection of HIV and cancer in both research and clinical practice (5). These HIV-associated cancers are divided into two groups: AIDS-defining cancers (ADCs), which include Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer and non-AIDS-defining cancers (NADCs), which include anal, lung, breast, and prostate cancers, among others (6, 7). Cancer development in PLWH is multifactorial, driven by immunosuppression, chronic inflammation, and co-infections with oncogenic viruses such as HHV-8, EBV, and HPV (8, 9). Even with well-controlled HIV, persistent immune activation and oxidative stress may sustain an elevated cancer risk (10). These mechanisms highlight the complexity of cancer pathogenesis in the context of HIV.

Sub-Saharan Africa (SSA) bears more than two-thirds of the global HIV burden, underscoring the region's disproportionate vulnerability to HIV-related morbidity and mortality (11). South Africa, in particular, has an estimated 7.8 million PLWH and an adult prevalence rate of 17.2% (12). Limited healthcare infrastructure, socioeconomic challenges, and a high prevalence of co-infections compound the high burden of HIV in SSA. Projections estimate that nearly one million cancer-related deaths will occur annually in sub-Saharan Africa by 2030, mainly driven by HIV and associated comorbidities (13, 14). Delays in diagnosis and limited access to treatment further exacerbate outcomes for individuals affected by both HIV and cancer.

Residual immune dysfunction and chronic inflammation contribute to persistent cancer risk despite antiretroviral therapy. This process, termed "inflammaging," refers to chronic, low-grade inflammation associated with accelerated immunological ageing (15, 16). Understanding these mechanisms may inform future therapeutic strategies. Although recent advances in cancer immunotherapy, such as immune checkpoint inhibitors, show promise, they remain largely inaccessible in resource-limited settings (17). Evaluating their feasibility and effectiveness in people living with HIV is an emerging research priority.

This review synthesises current evidence on HIV-associated cancers in sub-Saharan Africa, examining both AIDS-defining and non-AIDS-defining malignancies. It highlights biological, structural, and social determinants, including HIV subtype C, co-endemic infections such as tuberculosis and malaria, genetic diversity, stigma, and inequality. The review also identifies research gaps and outlines strategies to integrate cancer care within existing HIV programmes.

This review was conducted as a narrative synthesis of published literature. We searched PubMed, Scopus, Web of Science, and ScienceDirect for publications from January 2014 to October 2025. Google Scholar was additionally searched to capture regional and grey literature. Reports from major international organisations, including the World Health Organisation (WHO), UNAIDS, and the International Agency for Research on Cancer (IARC), were also reviewed for epidemiological and policy data relevant to sub-Saharan Africa. Search strategies used combinations of keywords and logical connectors to refine results. Core terms included HIV-associated cancer, AIDS-defining cancers, non-AIDS-defining cancers, sub-Saharan Africa, and cancer disparities. Additional terms, such as immunosuppression, chronic inflammation, co-infections, and the tumour microenvironment, were also applied. We included original research articles, reviews, and systematic reviews addressing cancer incidence, pathogenesis, clinical outcomes, or healthcare disparities among people living with HIV in sub-Saharan Africa. Case reports and non-peer-reviewed editorials were excluded. Evidence was synthesised narratively and analysed thematically to explore the intersection of HIV and cancer, integrating epidemiological, clinical, and molecular findings with emerging advances in immunotherapy and integrated care models for resource-limited settings.

2. AIDS-Defining Cancers

The widespread use of antiretroviral therapy has transformed the HIV landscape and altered the spectrum of HIV-associated malignancies. However, AIDS-defining cancers, including Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), and invasive cervical cancer, remain a major clinical challenge in sub-Saharan Africa, where HIV prevalence is highest (18). This section explores the continued high burden of ADCs in SSA. It focuses on regional drivers such as endemic oncogenic viruses, co-occurring infections such as tuberculosis and malaria, and structural barriers within the health system. These factors contribute to aggressive disease phenotypes and poor outcomes, despite the scale-up of ART.

2.1 Kaposi Sarcoma

Kaposi sarcoma (KS), a vascular tumour of lymphatic endothelial origin, remains the most common HIV-associated malignancy in sub-Saharan Africa. Its development is driven by human herpesvirus 8 (HHV-8), which is endemic in the region and becomes oncogenic in the context of HIV-induced immunosuppression.

2.1.1 Epidemiology and Disparities

The global distribution of Kaposi sarcoma highlights significant health disparities, with SSA experiencing a disproportionately high burden due to HIV co-infection. In 2020, over 34,000 KS cases were estimated globally, all attributable to KSHV; approximately 80% of cases in SSA were linked to HIV, compared to only 50% in the rest of the world (19). The burden shows remarkable regional variation within Africa. Southern Africa carries the highest burden, with HIV co-infection rates among KS patients approaching 93% in South Africa and Botswana. Eastern Africa follows with substantial prevalence (76.7%), ranging from 63.4% in Zambia to 100% in Kenya (19, 20). Western and Central African nations, including Nigeria and Cameroon, show moderately high HIV prevalence in KS cases at 74.9% and 72.1% respectively. This contrasts sharply with Northern Africa, where HIV prevalence among KS cases remains around 3.0%, a pattern mirrored in South-Central and Western Asia (19). High-income countries demonstrate attenuated but clinically significant associations. During the ART era, the United States documents HIV co-infection in 73.7% of KS cases, closely mirroring Australian reports of 75.0% prevalence (19, 20). European surveillance reveals substantial regional variation, with Northern and Western Europe reporting elevated prevalence (approximately 71.5%) compared to substantially lower rates throughout Southern, Central, and Eastern Europe (averaging 46.7%). Asian populations exhibit markedly reduced associations, with Eastern Asia documenting 21.8% prevalence and South-Central/Western Asia reporting minimal co-infection rates of 7.7%, with particularly low incidence in Turkey (5.4%), Iran (3.7%), and Israel (3.7%) (19).

The epidemiological trajectory of KS has undergone a significant transformation following the widespread implementation of ART. Numerous populations, including White Americans, Israelis, Ugandans, Costa Ricans, Colombians, Canadians, and Danish cohorts, have experienced substantial declines in KS incidence, directly attributable to effective ART coverage and comprehensive HIV prevention initiatives (21). However, this positive trend shows notable exceptions, with significant incidence increases observed among males in

Türkiye (AAPC 11.5%) and the Netherlands (AAPC 2.5%), likely reflecting epidemiological shifts in at-risk populations and altered KSHV transmission dynamics, particularly among men who have sex with men (MSM) (20). Persistent racial disparities remain evident even in high-resource settings. Within the United States, Black/African American individuals with HIV experience dramatically elevated KS incidence, demonstrating age-adjusted rates of 36.7 per 100,000 person-years compared to 8.9 per 100,000 person-years in the general population, highlighting profound racial inequities in KS risk stratification (22). This pattern of disproportionate burden extends to European contexts, with long-term observational studies in Italy confirming KS represents 68.3% of all AIDS-defining malignancies among HIV-positive individuals, emphasising the continued regional significance of this malignancy even within well-resourced healthcare systems (23).

The persistent KS burden in SSA, despite the availability of ART, reflects complex, multifactorial challenges. The region's high background HHV-8 seroprevalence, often established during childhood, creates substantial viral reservoirs that are primed for reactivation during immunosuppression. Compounding this biological vulnerability, frequent late HIV diagnosis and advanced immunosuppression at ART initiation create optimal conditions for KS development and progression. The clinical presentation in SSA often involves more aggressive disease phenotypes, characterised by extensive cutaneous involvement and frequent visceral dissemination, contributing to complex management challenges and substantially poorer outcomes compared to high-income settings.

An unresolved question that critically limits progress is the role of specific KSHV genetic variants and host immunogenetic factors in driving the aggressive disease phenotype observed in SSA. Many molecular studies on KSHV have focused on viral strains from Europe and North America, leaving a profound gap in our understanding of KSHV virology in African populations. Similarly, the impact of host genetics, such as specific HLA polymorphisms common in African ancestries, on the immune response to HHV-8 and the risk of KS progression remains virtually unexplored. Elucidating these factors is essential for understanding the fundamental biology of KS in SSA and could inform risk stratification

2.1.2 Clinical Subtypes and Pathophysiological Mechanisms

KS manifests in four distinct epidemiological subtypes, all of which share a common pathophysiological basis in infection with Human Herpesvirus 8 (HHV-8). The classic variant typically affects HIV-negative, middle-aged to older adults of Mediterranean, Eastern

European, or Middle Eastern descent. The endemic form occurs in HIV-negative individuals in sub-Saharan Africa and may be influenced by cofactors such as malaria and malnutrition, which compromise immune function (24, 25). The iatrogenic subtype occurs in transplant recipients receiving immunosuppressive therapy, while the AIDS-related form is the most common presentation among people living with HIV. This phenotype is typically associated with advanced immunosuppression and often reflects AIDS stage (24) (20).

Despite their varied clinical presentations, all subtypes of Kaposi sarcoma are caused by HHV-8, which establishes latency in endothelial cells. Reactivation occurs under conditions of immunosuppression, whether due to HIV-mediated CD4+ T-cell depletion, immunosuppressive therapy, or other factors that impair immune surveillance. These conditions ultimately drive oncogenesis (25, 26). The molecular pathogenesis of Kaposi sarcoma involves latent HHV-8 proteins, including LANA (Latency-Associated Nuclear Antigen), vCyclin, and vFLIP, which promote cell survival, inhibit apoptosis, and induce proangiogenic inflammation. The lytic protein vGPCR further contributes by driving angiogenic signalling (25, 27, 28). In people living with HIV, CD4+ T-cell depletion and cytokine dysregulation contribute to a permissive microenvironment that enhances viral replication and spindle-cell proliferation. Severe cases, such as Kaposi Sarcoma–Associated Herpesvirus Inflammatory Cytokine Syndrome (KICS), are characterised by uncontrolled viral replication and systemic inflammation (29). Kaposi sarcoma lesions commonly affect the skin, mucous membranes, lungs, and gastrointestinal tract, reflecting the virus's broad tissue tropism. Notably, KS can develop even in individuals receiving ART with partial immune recovery, indicating that its pathogenesis involves complex virus–host interactions beyond immunosuppression alone (29).

2.2 Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma (NHL) is among the most common malignancies in people living with HIV. Its pathogenesis is primarily driven by oncogenic viruses such as Epstein–Barr virus (EBV), with HIV-related immunosuppression amplifying the risk. PLWH have a markedly increased risk of NHL, with a pooled relative risk approximately 23.5 times higher than that of HIV-negative individuals. In 2019, an estimated 6.9% of new global NHL cases (around 30,500) were attributable to HIV infection, representing a threefold increase since 1990 (30). In sub-Saharan Africa, the heightened risk of non-Hodgkin lymphoma reflects a complex interplay between HIV-related immunosuppression, opportunistic infections, and distinct biological characteristics of HIV-associated lymphomas. Understanding these factors is

essential for informing targeted interventions to reduce the growing burden of NHL in the region (30, 31).

2.2.1 Epidemiology and Disparities

The burden of HIV-associated NHL in sub-Saharan Africa is evident in clinical practice, with reports from some regional hospitals indicating HIV seropositivity rates exceeding 70% among adult NHL patients (32). Aggressive, high-grade B-cell lymphomas and frequent late-stage diagnoses characterise this clinical presentation. Patient outcomes are significantly affected by constrained healthcare infrastructure and delays in initiating appropriate treatment (33).

Eastern and Southern Africa collectively account for approximately 44.5% of global HIV-associated NHL cases, a burden attributable primarily to the region's high HIV prevalence and persistent healthcare inequities. In contrast, Eastern Europe and Central Asia have experienced the most rapid increase in incidence, with an annual growth rate of 8.7% between 2010 and 2019 (30). While antiretroviral therapy has reduced NHL incidence in high-income countries, PLWH retain a markedly elevated risk compared to the general population.

Significant racial and socioeconomic disparities in NHL persist globally. In the United States, Non-Hispanic Whites have the highest overall NHL incidence, yet Non-Hispanic Black women show the steepest upward trend. Environmental factors such as exposure to pollutants and urban living conditions may contribute to the elevated burden among African Americans (34). Among Hispanic populations, specific B-cell and T-cell lymphoma subtypes occur at higher rates than in non-Hispanic groups (34). Globally, both the incidence and mortality of NHL are increasing more rapidly in low- and middle-income regions, highlighting ongoing healthcare inequities (35).

The high burden of HIV-associated non-Hodgkin lymphoma in Africa cannot be explained by HIV prevalence alone. The aggressive clinical behaviour and poor outcomes observed suggest the influence of region-specific cofactors. A potential triple hit involving HIV, Epstein-Barr virus, and endemic infections such as malaria and tuberculosis may drive chronic antigenic stimulation, accelerating B-cell transformation. In addition, host genetic diversity in African populations could modulate susceptibility through variations in immune regulation and cytokine profiles. The predominance of HIV-1 subtype C in sub-Saharan Africa, which may have distinct immunopathogenic characteristics, also remains underexplored. These factors highlight the need for regionally tailored research to elucidate lymphoma pathogenesis in African contexts better.

2.2.2 Pathophysiological mechanisms

The pathogenesis of HIV-NHL is a multifactorial process involving immunosuppression, chronic inflammation, and viral oncogenesis. HIV leads to significant immunosuppression, characterised by a decline in CD4+ T-cell counts, which is directly correlated with increased cancer incidence. This association is quantitatively significant; every 100 cells/μL decrease in CD4 count is associated with an adjusted hazard ratio of 1.18 for the development of non-Hodgkin lymphoma, as reported by Ruffieux et al. (36). Depletion of CD4+ T cells compromises immune surveillance against oncogenic viruses such as EBV. In parallel, CD8+ T cells exhibit functional exhaustion, characterised by upregulation of inhibitory receptors, including PD-1 and CTLA-4, which impairs cytotoxic responses against malignant cells (37, 38). Although ART improves immune function, residual dysfunction and persistent viral reservoirs sustain an elevated NHL risk (Figure 1).

The pathogenesis of HIV-associated NHL extends beyond immunosuppression to include chronic B-cell activation and cytokine dysregulation. Persistent HIV antigenemia drives sustained immune activation, resulting in B-cell hyperactivation. This is reflected by elevated serum levels of immunoglobulin free light chains, neopterin, and pro-lymphomagenic cytokines such as interleukin-6 (IL-6), interleukin-10 (IL-10), and tumour necrosis factor-alpha (TNF-α), which collectively create a permissive environment for lymphomagenesis and suggest that immune activation precedes NHL development. Notably, this inflammatory milieu persists despite antiretroviral therapy and continues to contribute to lymphoma risk (37, 39).

Opportunistic infections with lymphotropic viruses, particularly Epstein-Barr virus (EBV) and Kaposi's sarcoma-associated herpesvirus, contribute significantly to the pathogenesis of HIV-associated non-Hodgkin lymphoma. EBV plays a central role through the expression of latent membrane proteins LMP1 and LMP2A, which activate pro-survival and proliferative signalling pathways such as NF-κB and facilitate immune evasion in subtypes including diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma (32). Similarly, KSHV encodes oncogenic proteins, such as latency-associated nuclear antigen (LANA) and FLICE-inhibitory protein (vFLIP), which disrupt cell cycle regulation and promote survival in primary effusion lymphoma (PEL) (8).

In addition to co-infecting viruses, HIV itself contributes directly to oncogenesis. HIV-1 proteins, including Tat, gp120, and p17, have been shown to induce DNA damage and

oxidative stress and to activate oncogenic pathways such as Akt, thereby enhancing the tumorigenic potential of infected and surrounding cells (38, 40). These direct effects of HIV synergise with viral cofactors to promote lymphomagenesis.

Mechanisms of HIV-induced cancer development

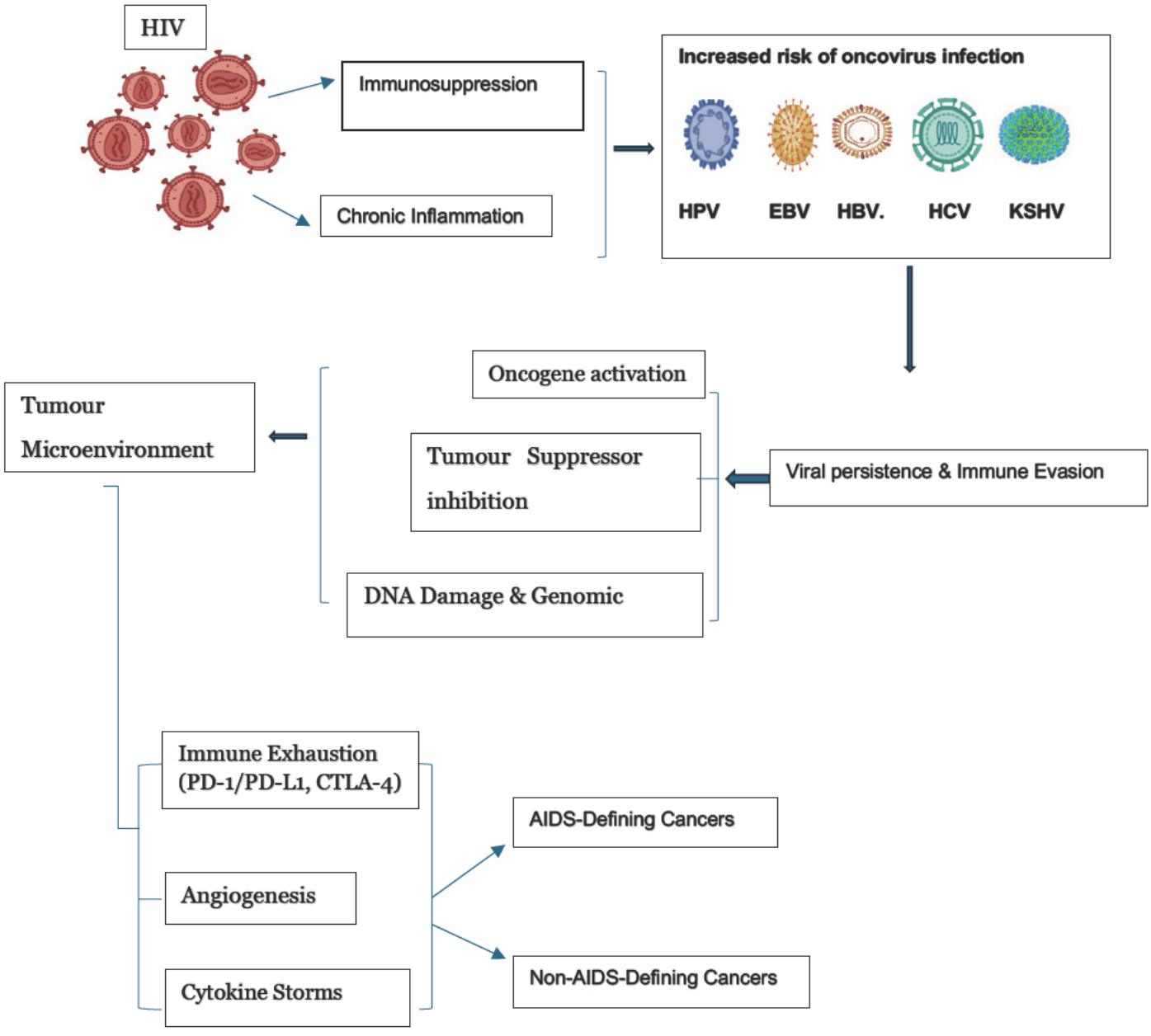

Figure 1. Mechanisms Driving Cancer Development in HIV Infection. HIV infection promotes cancer development through immunosuppression, chronic inflammation, oncogenic viral co-infections, and alterations in the tumour microenvironment, ultimately leading to AIDS-defining and non-AIDS-defining cancers.

2.3 Cervical cancer

Cervical cancer is the fourth most diagnosed cancer and the fourth leading cause of cancer-related death among women worldwide. However, this global figure masks substantial regional disparities. In sub-Saharan Africa, cervical cancer is often the leading cause of cancer mortality in women. This elevated burden is driven by a syndemic of high-risk human papillomavirus (HPV) infection, HIV co-infection, and systemic healthcare limitations. HIV-related immunosuppression increases HPV persistence and oncogenic potential (41, 42).

2.3.1 Epidemiology and Disparities

Cervical cancer is the fourth most common cancer among women worldwide and remains a major global health concern. In 2022, an estimated 662044 new cases and 348709 deaths occurred globally, with 84–85% of cases and 90% of deaths in low- and middle-income countries (LMICs), reflecting marked disparities in prevention and treatment (14, 43). Sub-Saharan Africa bears the highest incidence and mortality rates globally, underscoring the urgent need for targeted interventions (43). Women living with HIV (WLWH) have around six times the risk of developing cervical cancer compared to HIV-negative women, with HIV implicated in approximately 5% of cases globally. This burden is heavily concentrated among women aged 40 years and older, who account for over 85% of cases and deaths. Incidence and mortality rates in this age group are approximately 10 and 20 times higher, respectively, than among younger women (14, 43). This synergistic relationship is bidirectional. Women with HPV are twice as likely to acquire HIV, and WLWH face a much higher risk of persistent HPV infection. Early initiation of antiretroviral therapy significantly reduces the incidence and progression of precancerous cervical lesions (44-46).

The burden of HIV-associated cervical cancer is predominantly concentrated in Africa. In southern Africa, nearly 64% of women diagnosed with cervical cancer are living with HIV, while in East Africa, this proportion is approximately 27%. Countries such as Eswatini, Lesotho, Botswana, South Africa, and Zimbabwe exhibit rates exceeding 60%. This represents one of the highest HIV-attributable fractions for any cancer globally, with incidence rates exceeding 20 per 100,000 women in high-prevalence countries like Eswatini and Zimbabwe. In contrast, most other countries globally report proportions below 5% (45).

Regional studies confirm this substantial burden. In Northwest Ethiopia, nearly one-quarter (24.9%) of WLWH were diagnosed with cervical cancer, with risk factors including low CD4 counts and poor ART adherence (47). In Nigeria, 19.7% of women with invasive cervical

cancer were HIV-positive; they were younger and presented with more advanced disease (48). Similarly, in Cameroon, nearly 25% of cervical cancer patients were HIV-positive, often diagnosed at late stages (49). Despite this need, screening uptake remains low, with estimates indicating only 30% coverage in Sub-Saharan Africa (50). A massive implementation failure compounds this biological vulnerability. The burden of cervical cancer among women living with HIV in sub-Saharan Africa is exacerbated by critical health system limitations. WLWH often face multiple barriers to accessing care, including stigma, financial constraints, and geographic inaccessibility. These challenges complicate the timely initiation of treatment and continuity of care, frequently resulting in delayed diagnosis and presentation at advanced stages of disease (51, 52).

These disparities extend to high-income countries. In the United States, WLWH experience cervical cancer incidence rates 1.47 times higher for adenocarcinoma and 3.62 times higher for squamous cell carcinoma compared to the general population (53). These findings reveal the multifaceted and elevated risks that WLWH face worldwide, emphasising the urgent need for comprehensive, integrated strategies that combine effective HIV treatment, vaccination, regular screening, and education.

2.3.2 Pathophysiological mechanisms

HIV-induced immunosuppression, characterised by CD4+ T-cell depletion, facilitates the persistence of high-risk human papillomavirus (HPV) infections, particularly types 16 and 18, by impairing the cell-mediated immune response required for viral clearance. Persistent infection with oncogenic HPV types is a necessary cause of cervical cancer. The viral E5, E6 and E7 oncoproteins disrupt normal cell cycle regulation by inactivating tumour suppressor proteins p53 and retinoblastoma protein (pRb), thereby promoting malignant transformation (54, 55). This mechanistic synergy between HIV-induced immunosuppression and persistent high-risk HPV infection manifests clinically as more aggressive disease. Women living with HIV not only have a higher prevalence of high-risk HPV infections but are also more likely to be co-infected with multiple oncogenic HPV types. Furthermore, they experience a significantly faster progression from HPV infection to invasive cervical carcinoma compared to HIV-negative women. These findings underscore the need for intensified screening and prevention strategies tailored to this high-risk population

HIV-mediated depletion of CD4+ T cells severely compromises the cell-mediated immune response necessary for controlling and clearing HPV infections. This allows for persistent

high-risk HPV (hrHPV) infection, higher viral loads, and accelerated progression from cervical intraepithelial neoplasia (CIN) to invasive carcinoma (46, 48). This HIV-HPV synergy involves chronic inflammation and immune dysregulation, which can upregulate oncogenic signalling pathways such as PI3K-AKT (46). This mechanistic synergy manifests clinically as more aggressive disease. WLWH not only have a higher prevalence of hrHPV infections but also a greater likelihood of infection with multiple hrHPV types and a significantly faster rate of progression to invasive carcinoma (56).

In addition to immune suppression, a state of chronic systemic inflammation and a high prevalence of co-infections common in HIV-positive populations contribute to genomic instability, further fostering an environment conducive to malignant transformation (10). Although antiretroviral therapy improves immune function, it does not fully restore normal immunity. Women living with HIV on long-term, effective ART remain at substantially increased lifetime risk, highlighting the need for ongoing, enhanced screening within HIV care (10, 57).

3. Non -AIDS Defining cancers

The success of antiretroviral therapy in transforming HIV into a chronic condition has altered the cancer landscape for people living with HIV. As this population ages, non-AIDS-defining cancers have become a major clinical and public health concern, now accounting for most malignancies and a leading cause of death. This shift, well documented in high-income countries, is increasingly evident in SSA, where high HIV prevalence, limited healthcare resources, and environmental cofactors create a complex health challenge.

Pathogenesis involves persistent immune activation and chronic inflammation, which create a procarcinogenic environment despite effective ART(58). Co-infections with oncogenic viruses, notably HPV and hepatitis viruses, act synergistically with HIV-related immunosuppression to elevate cancer risk (59, 60). In sub-Saharan Africa, endemic infections such as malaria and tuberculosis further contribute to immune dysregulation. Genetic diversity within African populations may influence cancer susceptibility by altering immune responses, drug metabolism, and DNA repair pathways. These factors promote conditions favourable to carcinogenesis and shape the region's distinctive profile of non-AIDS-defining cancers. However, the mechanistic understanding of how these region-specific cofactors interact remains limited, as most molecular studies have been conducted in European or North American cohorts.

Globally, evidence shows that ART-driven longevity has shifted the cancer profile among PLWH toward non-AIDS-defining malignancies. In Italy, Cattelan et al. reported that NADCs accounted for 57.4% of cancers among 289 PLWH over 28 years, with the mean age at diagnosis increasing from 41.6 to 54.4 years. While AIDS-defining cancers such as Kaposi sarcoma and non-Hodgkin lymphoma remained prevalent, the spectrum expanded to include hepatocellular carcinoma, anal, non-melanoma skin, breast, and prostate cancers. Simultaneous HIV and cancer diagnoses declined over time, reflecting earlier HIV detection and improved survival. Similarly, Anastasia et al. found that NADCs comprised 60.8% of 153 malignancies in HIV-positive patients over 25 years, occurring in older individuals and demonstrating mortality rates comparable to AIDS-defining cancers (23, 61).

These findings illustrate how ART-driven longevity is reshaping the cancer landscape among PLWH globally, a trend now emerging in sub-Saharan Africa, where evidence remains limited, but early signals suggest a similar epidemiological shift.

Regional variations significantly influence the incidence and outcomes of non-AIDS-defining cancers. In sub-Saharan Africa, the epidemiological pattern differs markedly from that observed in high-income countries. For example, liver cancer demonstrates a relatively low standardised incidence ratio (SIR = 0.81), whereas anal cancer shows a substantially elevated incidence (SIR = 28.33) and a very high standardised mortality ratio (SMR = 124.07) (62). These disparities reflect differences in exposure to oncogenic cofactors, limited diagnostic capacity, and unequal access to oncology care. Late-stage presentation and restricted availability of surgery, radiotherapy, and systemic therapies further worsen outcomes. Broader systemic barriers, including inadequate cancer registries, shortages of trained oncology personnel, and limited access to essential medicines, continue to constrain effective prevention and control efforts (63).

Despite increasing awareness, substantial data gaps persist regarding the burden and determinants of non-AIDS-defining cancers in sub-Saharan Africa, where high HIV prevalence intersects with limited cancer surveillance and treatment capacity. This review focuses on three of the most common and clinically relevant NADCs, breast, prostate, and anal cancers, examining their epidemiology, pathophysiology, and the unique disparities influencing outcomes in resource-limited settings.

3.1 Breast cancer

3.1.1 Epidemiology and Disparities

Globally, breast cancer remains a critical health issue, with an estimated 2.3 million new diagnoses and 670,000 deaths in 2022 (64). Women living with HIV experience pronounced disparities, presenting with more advanced tumours, a higher incidence of aggressive triple-negative breast cancer (TNBC), and poorer overall outcomes despite advances in treatment (59). These disparities are likely driven by delayed presentation and limited access to diagnostic imaging. Socioeconomic barriers delay early detection and treatment. WLWH experience a nine per cent lower three-year survival rate (46% vs 55%) and face a 41% increased mortality risk (65). In South Africa, the SABCHO study reported that women living with HIV had significantly lower two-year overall survival compared with HIV-uninfected women (72.4% vs 80.1%) (66). Expanding on this, Joffe et al., 2025 reported five-year overall survival of 44.3% (95% CI 42.5–46.2%) among 2,838 South African women with invasive breast cancer treated within the public health system. Key determinants of survival included late-stage diagnosis, incomplete or absent treatment, and HIV infection, highlighting the urgent need for earlier detection and improved access to care (67). A key driver is the higher prevalence of TNBC among WLWH, as demonstrated in a South African cohort where 21% of HIV-positive women had TNBC compared to 15% of HIV-negative women (68).

Beyond South Africa, survival rates across sub-Saharan Africa vary considerably. A recent meta-analysis of 49 studies estimated 1-, 3-, and 5-year survival at 79%, 56%, and 40%, respectively, with later studies reporting improvements to 46–47% for 5-year survival in post-2014 cohorts (69). Multiple contextual factors, including national development level, stage at diagnosis, access to treatment, and HIV prevalence shape survival. These findings emphasise the broader health and socioeconomic environment in which South African patients receive care and illustrate the variability in breast cancer outcomes across the region. Interestingly, this increased aggressiveness contrasts with incidence data from high-income countries. The French DAT' AIDS cohort found the standardised incidence ratio for breast cancer in WLWH was lower than the general population (SIR 0.6) (70). This paradox suggests that HIV may not increase the initial risk of breast cancer but fundamentally alters its biological behaviour and the host's antitumor response. Despite these insights, data from sub-Saharan Africa remain limited. Few population-based studies accurately capture the burden of breast cancer among women living with HIV. Additionally, the effectiveness and coverage of breast

cancer screening programs in this population are poorly characterised. Limited screening and early detection may exacerbate progression driven by chronic inflammation and immune dysregulation.

3.1.2 Pathophysiology and Clinical Aspects

The pathophysiological link is driven primarily by HIV-mediated immune dysregulation. Chronic systemic inflammation, characterised by elevated IL-6 and TNF-α, creates a tumour-promoting microenvironment that enhances proliferation, survival, and angiogenesis (71). This process is distinct from other HIV-associated malignancies, as it is not directly driven by oncogenic viruses like HPV or EBV (71). Chronic immune activation in women living with HIV is characterised by sustained elevations in cytokines such as IL-6 and TNF-α, which drive oncogenic signalling through STAT3 and NF-κB pathways. Elevated IL-6 levels, commonly observed in breast cancer, promote angiogenesis, epithelial-mesenchymal transition, and endocrine resistance, contributing to the aggressiveness of triple-negative subtypes. These mechanisms suggest that HIV-related inflammation may amplify tumour progression beyond the effects of viral oncogenesis (72). Evidence from Felcher et al. (2022) indicates that the broader IL-6 cytokine family, including IL-6, LIF, OSM, and IL-11, acts as a key regulator of tumour progression and metastasis through the gp130–JAK–STAT3 axis, highlighting potential targets for precision therapy (73). Premature immune senescence further compromises genomic stability and DNA repair mechanisms. Furthermore, the tumour immune microenvironment in WLWH is often immunosuppressive, featuring elevated PD-1/PD-L1 expression and reduced cytolytic T-cell activity, facilitating immune escape and tumour progression (figure 1) (74).

Clinically, immune status is a critical prognostic factor. Immune suppression, defined by CD4+ counts below 500 cells/mm³, is directly associated with a poorer prognosis and increased tumour aggressiveness (75). Emerging evidence suggests that factors such as chronic co-infections, adherence to antiretroviral therapy, and HIV viral load may influence tumour behaviour and treatment response. However, the underlying mechanisms remain poorly understood. This evidence underscores the necessity for tailored screening, diagnostic, and therapeutic strategies for this distinct patient population. However, important research gaps persist regarding optimal treatment strategies for women living with HIV. Evidence regarding interactions between antiretroviral therapy and chemotherapy, radiotherapy, or targeted therapies remains limited. Moreover, WLWH are frequently underrepresented in clinical trials. Long-term survivorship outcomes, including quality of life and treatment-related

complications, are poorly documented, particularly in low-resource settings. Future research should focus on clarifying the mechanistic links between chronic immune dysregulation and breast cancer progression in HIV-positive populations, identifying optimal treatment combinations, and developing strategies to improve long-term outcomes in resource-limited settings.

3.2 Prostate cancer

Prostate cancer is one of the common non-AIDS-defining cancers affecting people living with HIV. Although PLWH have an increased risk for virally mediated cancers, age-related cancers like prostate cancer are becoming more frequent and contribute significantly to morbidity and mortality. Ageing, behavioural, and HIV-specific factors influence prostate cancer risk and outcomes in this population (76). The relationship between HIV infection and prostate cancer risk is complex. It appears to vary significantly by geographic region and access to healthcare, reflecting disparities in screening practices and underlying biological factors.

3.2.1 Epidemiology and Disparities

Prostate cancer is a significant global health burden, with an estimated 1.5 million new cases and 397,000 deaths worldwide in 2022. Prostate cancer is a leading malignancy in men (14). The relationship between HIV infection and prostate cancer risk demonstrates substantial epidemiological complexity, with meta-analyses frequently reporting either comparable or reduced incidence among PLWH. One comprehensive analysis indicated a 24% lower risk of prostate cancer in PLWH compared to HIV-negative populations (62, 77, 78). This observed risk reduction represents an epidemiological paradox primarily attributable to healthcare disparities rather than biological protection. The apparent protective effect is substantially diminished in settings with equitable healthcare access, suggesting systematic differences in detection methods.

A pivotal South African cohort study demonstrated a 35% lower unadjusted prostate cancer diagnosis rate among men with HIV. However, after adjusting for disparities in PSA testing availability and biopsy rates, this association completely disappeared, showing no evidence of biological risk reduction (79). These findings are corroborated by the Veterans Ageing Cohort Study, which established that PLWH undergo significantly fewer PSA screenings and biopsy procedures. After statistical adjustment for these screening disparities, prostate cancer incidence rates between PLWH and HIV-negative comparators became equivalent (80). Recent data from high-resource settings suggest that the previously lower incidence of

prostate cancer among people living with HIV is gradually increasing as this population ages, particularly in the United States, where prostate cancer is projected to become the most diagnosed tumour in this group. Tumour characteristics and stage appear broadly similar to those in HIV-negative individuals; however, optimal early detection strategies remain under evaluation, and HIV-specific guidance for PSA-based screening is limited (81).

The collective evidence indicates that the observed epidemiological pattern of reduced prostate cancer incidence in PLWH primarily reflects disparities in cancer screening practices rather than genuine biological differences in susceptibility. These findings underscore the critical importance of addressing healthcare access inequalities and implementing standardised screening protocols for PLWH to ensure equitable cancer detection and management.

3.2.2 Pathophysiology and Clinical Aspects

Despite the epidemiological paradox, the pathogenesis of prostate cancer in PLWH involves a complex interplay of viral persistence, chronic immune dysregulation, and tumour microenvironment remodelling. A chronic pro-inflammatory milieu, characterised by elevated levels of IL-6, TNF-α, and other mediators, persists despite effective ART and creates a persistent tumour-promoting environment that facilitates cellular transformation and progression (9, 59).

The prostate tumour microenvironment in PLWH exhibits exaggerated immunosuppressive characteristics. There is substantial infiltration of myeloid-derived suppressor cells (MDSCs) and M2-polarised tumour-associated macrophages (TAMs), which create an immune-evasive niche. Concurrently, HIV-specific T-cell exhaustion, marked by increased expression of PD-1, PD-L1, and TIM-3, severely compromises antitumor immunosurveillance (82, 83).

Notably, ART introduces additional complexity. Some ART drugs can influence androgen levels and suppress PSA production, potentially complicating screening and contributing to delayed diagnoses and more advanced disease at presentation (59). A higher prevalence of hypogonadism in PLWH may further alter the hormonal landscape of prostate carcinogenesis (84). This pathophysiological framework of chronic inflammation, immune evasion, and diagnostic challenges explains the more aggressive clinical behaviour and worse outcomes observed in HIV-associated prostate cancer. Clinical studies further suggest that treatment patterns and tolerability in PWH are broadly similar to those in the general population. However, disparities in access to surgery, radiation, and hormone therapy exist. Recent

analyses indicate that prostate-cancer-specific mortality may not differ substantially from that of HIV-negative individuals. However, all-cause mortality may remain elevated due to comorbidities and delayed diagnosis. Emerging evidence suggests that androgen levels and hypogonadism may partly influence prostate cancer risk in people with HIV.

In contrast, immune dysfunction appears less directly involved than in other HIV-associated malignancies. These observations highlight the need to monitor hormonal status and consider individualised screening strategies in this population (81). Most studies on prostate cancer in people living with HIV have been conducted in high-resource settings, with limited representation of African populations. Given the substantial genetic diversity, variation in HIV subtypes, and differences in environmental and healthcare factors across the continent, the applicability of existing findings to African populations remains uncertain. Addressing these gaps is essential for developing context-specific strategies for screening, prevention, and management.

3.3 Anal cancer

3.3.1Epidemiology and Disparities

Squamous cell carcinoma of the anus (SCCA), the most common histologic subtype, is universally associated with persistent human papillomavirus infection, which causes over 90% of cases (85). HIV co-infection significantly potentiates HPV oncogenicity, substantially elevating SCCA risk among PLWH (86). This risk manifests in a substantial global burden; in 2020, an estimated 20.7% of all new SCCA cases in men and 2.8% in women occurred among PLWH (87). Reflecting this disparity, the global age-standardised incidence rate (ASIR) of HIV-associated SCCA was higher in men (0.07 per 100,000 person-years) than in women (0.02) (87).

Geographically, SCCA cases in HIV-positive men were concentrated in North America (34%), Europe (22%), and Africa (17%), while most cases in women (68%) were concentrated within sub-Saharan Africa. Proportions reached extreme levels in Southern Africa, where 78.9% of male and 63.2% of female SCCA cases occurred among PLWH(87). Regional clinical data further show this elevated risk. A 12-year study from the U.S. Southeast reported an anal cancer incidence of 258 per 100,000 person-years among PLWH, with 79% of cases diagnosed before age 55 (88). The burden is highest among men who have sex with men (MSM); U.S. population-based data show that MSM living with HIV, particularly those with an AIDS diagnosis, face the most significant cumulative risk (89).

Despite this, considerable screening gaps persist, with many patients lacking recent anal cytology testing before diagnosis (86, 88). While the current burden is highest in high-income countries, incidence is expected to rise in low-income countries due to higher HPV prevalence and lower vaccine coverage, highlighting the urgent need for global prevention strategies (85).

3.3.2 Pathophysiology and Clinical Aspects

The pathogenesis of anal squamous cell carcinoma (SCC) in PLWH represents a multifactorial process involving complex viral and immunological interactions. The central mechanism involves synergistic oncogenesis between persistent HPV infection and HIV-induced immunosuppression (86, 90). HIV-mediated CD4+ T-lymphocyte depletion profoundly compromises cell-mediated immunity, creating a permissive environment for HPV persistence and progression to high-grade anal intraepithelial neoplasia (AIN2/3), the recognised precursor lesion to invasive SCC(90). Furthermore, HIV proteins exert direct oncogenic effects: the Tat protein promotes cellular proliferation and angiogenesis by activating NF-κB and upregulating VEGF, while the Nef protein inhibits apoptosis by modulating p53 and Bcl-2, allowing survival of malignantly transformed cells (9, 10). Impaired immune surveillance significantly reduces the clearance rates of high-risk HPV genotypes (HPV-16 and -18), thereby enabling enhanced oncogenic expression (90).

The chronic inflammatory state characteristic of HIV infection further promotes carcinogenesis. Persistent immune activation leads to sustained production of inflammatory cytokines (TNF-α, IL-6, IL-1β), which induce cellular proliferation, inhibit apoptosis, and cause DNA damage. This state also generates reactive oxygen species (ROS) that foster genomic instability (9, 10). Additionally, HIV infection accelerates immune ageing, characterised by depletion of naïve T-cells and accumulation of exhausted, ineffective T-cells that compromise immune surveillance (9). The tumour microenvironment in PLWH exhibits substantial immunosuppressive characteristics that facilitate immune evasion. This includes increased infiltration of regulatory T cells (Tregs) and upregulation of immune checkpoint markers (PD-1/PD-L1), leading to adaptive immune resistance (86). The combination of viral oncogenesis, direct HIV protein effects, chronic inflammation, genomic instability, and profound immunosuppression creates a synergistic multifactorial process that accelerates carcinogenesis. This multifaceted mechanism explains the markedly elevated SCC incidence, earlier presentation, and more aggressive progression observed in PLWH (9, 10, 86, 90).

Table 1: Global Variation in Cancer Burden: Comparative 5-Year Prevalence Across Continents (GLOBOCAN 2022)

Continent	Cervical	Anal	Kaposi Sarcoma	NHL	Prostate	Breast
Africa	40.7	0.98	3.9	9.4	27.6	72.2
Latin America & Caribbean	58.6	2.5	1.2	20.4	179.6	214.3
Northern America	32.6	9.3	1.1	81.3	604.4	706.7
Europe	53.8	6.3	1.1	57.6	530.2	594.5
Oceania	35.4	6.2	0.43	58.3	468.4	548.4
Asia	52.2	0.97	0.14	15.3	47.0	140.6

Values represent 5-year prevalence per 100,000 population. Breast cancer is reported for females; all other cancers include both sexes.

Table 2. Prevalence and incidence of major HIV-associated cancers across African, Caucasian, and Asian populations, highlighting regional disparities

Cancer Type	Metric	Africa		Caucasian		Asian	
		Africa PLWH	General Population	PLWH	General Population	PLWH	General Population
Kaposi Sarcoma	Prevalence	80–100% of KS patients HIV+(South Africa, Botswana, Kenya)[19]	Endemic in Southern & Eastern Africa; highest in Mozambique, Zambia, Uganda[91]	47–74% of KS patients HIV+ (U.S., Europe, Australia)[19]	<10%	21% Eastern Asia7.7% South-Central & North Asia Iran 3.7%, Turkey 5.4%[19]	<10%
	Incidence / ASIR	—	Africa: 2.2 per 100,000 (Males 3.0, Females 1.5); highest in Mozambique, Zambia, Uganda [20]	—	Italty:1.3 per 100,000 Black American:1.9(20)	—	<0.01 per 100,000 (India, Sri Lanka)[20]
Non-Hodgkin Lymphoma (NHL)	PAF	44.46% Eastern & Southern Africa[30]	—	3.08% Western & Central Europe, North America[30]	—	1.97% Asia & Pacific(30)	—

Cervical Cancer	Prevalence / ASIR	ESwatini 75%, Botswana66.55%, South Africa 63.4%[45] Nigeria 19.7%[48], Cameroon 24.67%[49]	ASR:6.5-40.42/100,000 (Africa) (Wu et al., 2025)	America and Europe5-5.3%[92] USA:1% [53]	ASR:6.35-15.74/100,000 (Europe and America)[43] USA:99% [53]		
	PAF	—		—	—	PAF:1.4%[45]	—
Anal Cancer (SCCA)	Proportion HIV+	Sub-Saharan Africa: 36.0% (men), 24.6% (women)Southern Africa: 78.9% (men), 63.2% (women) [87]	8.7%[93]	U.S.: 34% (men HIV+), Europe: 22% (men HIV+)[87]	Europe: 29.5% [93] Northen America:10.3-21.7%[93]	Low proportion linked to HIV [87]	28.2% [93]
Breast Cancer	Proportion HIV+ / SIR	Sub-Saharan Africa: 19%[65]	20–60% (South Africa, Kenya, Zimbabwe) [91]	France : SIR: 0.6 (0.4–0.7) [70]	High incidence >80 per 100,000		Low[91]

					(N. America & Europe) [91]		
Prostate Cancer	Proportion HIV+ / Incidence	South Africa: 7%[79]	Incidence: 12.6 per 100,000 (Transitioning countries) [14]	France: SIR: 0.6 (0.5–0.7) [70] US: Lower incidence[81]	Incidence: 35.5 per 100,000 (Transitioned countries avg.; highest globally in N. Europe, Australia/NZ, N. America) [14]	—	Lowest incidence [14]

ASIR refers to the age-standardised incidence rate per 100,000 women; PAF indicates the population-attributable fraction; transitioned countries are high-income settings with established cancer control programs, whereas transitioning countries are low- and middle-income settings with developing cancer control programs;

3. Discussion

The landscape of HIV-associated malignancy in sub-Saharan Africa reflects a dual burden: the continued presence of AIDS-defining cancers alongside a rising incidence of non-AIDS-defining cancers. This pattern does not represent a transition from one era to another but rather the simultaneous persistence of both cancer types. Evidence suggests that this duality is driven by the region's unique epidemiological and biological context, compounded by systemic health inequities. The result is not only an increase in cancer incidence but also a more aggressive disease phenotype, shaped by a syndemic of oncogenic viruses, chronic immune dysregulation, and structural barriers to care.

The continued high burden of ADCs underscores that ART scale-up, while life-saving, has not eliminated HIV-related malignancies. KS remains a sentinel cancer, with HIV co-infection rates among KS patients in Southern Africa approaching 93%, compared with 47–74% in Western cohorts (94). This disparity reflects the high endemicity of HHV-8 and is compounded by late HIV diagnosis and advanced immunosuppression at ART initiation. Similarly, the high proportion of HIV-associated non-Hodgkin lymphoma and cervical cancer, where up to 75% of cervical cancer patients are living with HIV in countries such as Eswatini (45), signals critical gaps in secondary prevention. HIV-induced immunosuppression impairs control of oncogenic viruses, including HHV-8, EBV and HPV. However, the persistence of ADCs ultimately reflects systemic failures: limited access to early HIV testing, inadequate HPV screening among women living with HIV, with uptake as low as 30% in the region (50), and delays in oncology referral. The high prevalence of KS, NHL and cervical cancer in sub-Saharan Africa (Tables 1 and 2) is not merely epidemiological data; it is a measure of health system inequity.

The emergence of non-AIDS-defining cancers as a leading cause of morbidity and mortality among PLWH is an unambiguous sign of the success of ART. However, it exposes a new layer of vulnerability. As the population of PLWH ages, they face a cancer risk profile shaped not only by immunosuppression but also by chronic immune activation and inflammation, or inflammaging, which persists even with virological suppression. This review highlights a critical pattern: for common NADCs such as breast and prostate cancer, the issue is not necessarily higher incidence but significantly worse outcomes.

Breast cancer illustrates this disparity. Women living with HIV (WLWH) in high-income countries may have a lower incidence (SIR 0.6) (70), yet evidence from sub-Saharan Africa shows a different reality. WLWH present with more advanced disease and have significantly higher mortality, with a 41% increased risk of death and a nine per cent lower three-year survival rate (46% versus 55%) (65). A higher prevalence of aggressive triple-negative subtypes and diagnostic delays drives this. Prostate cancer reveals another disparity related to diagnostic bias. The apparently lower incidence of prostate cancer among PLWH in South Africa (79) and the United States (80) disappears after adjustment for PSA testing rates. This indicates that the observed protection is an artefact of inequitable access to screening, leading to underdiagnosis and potentially more advanced disease at presentation. In contrast, anal cancer represents a clear and direct threat, with an alarmingly high standardised incidence ratio (SIR 28.33) and mortality ratio (SMR 124.07) in PLWH (95).Yet it remains largely unaddressed by screening programmes in sub-Saharan Africa. The very high prevalence of breast cancer in the general population of the region (Tables 1 and 2) underscores that PLWH are ageing into a pre-existing cancer crisis, which HIV exacerbates.

A consistent and concerning theme across both ADCs and NADCs in this review is the aggressive clinical phenotype observed in sub-Saharan Africa. Cancers in PLWH in this region are characterised by a later stage at diagnosis, more aggressive histology, such as a higher prevalence of triple-negative breast cancer (68) and high-grade B-cell lymphomas in non-Hodgkin lymphoma (32) (33), and significantly poorer survival outcomes (65-67). This SSA phenotype cannot be explained by HIV alone. It is the product of a complex set of factors:

- Viral and biological cofactors: The high prevalence of oncogenic viruses, the potential impact of HIV subtype C and the unexplored role of host genetic diversity create a unique biological milieu.
- Endemic co-infections: The triple hit of HIV, EBV and endemic infections such as malaria and tuberculosis may drive chronic antigenic stimulation and B-cell activation, accelerating lymphomagenesis (31) (38).
- The inflammatory milieu: Persistent immune activation, even on ART, creates a tumour-promoting environment rich in IL-6 and TNF-α, which can drive oncogenic signalling and suppress anti-tumour immunity (9, 10) (58) (71).

- Health system limitations: These biological vulnerabilities are amplified by systemic failures, including limited diagnostic capacity, shortages of specialised oncology staff and fragmented referral pathways that cause critical delays (13) (50)

Cancer in Sub-Saharan Africa remains underreported due to systemic gaps that render it a silent killer. Underreporting is compounded by global health priorities favouring infectious diseases like HIV and TB, which receive robust funding and research. Consequently, cancer research funding is disproportionately directed to high-income countries, despite Africa's unique and growing cancer burden. Achieving equitable cancer control requires targeted investment in Africa to explore its genetic diversity, unique viral variants, and interactions with endemic infections. Africa's diversity is not a confounder; it is an opportunity to advance novel cancer biology and develop context-specific solutions. This area urgently needs dedicated funding.

4. Conclusion and Future Directions

The success of antiretroviral therapy in transforming HIV into a chronic condition has introduced a new challenge: the rising burden of cancer among people living with HIV, particularly in sub-Saharan Africa. Programmatic success should no longer be measured solely by viral suppression; extended lifespan must be accompanied by quality of life, requiring integrated care that prioritises cancer prevention and control.

Cancer services should be embedded within HIV programmes, leveraging existing infrastructure for HPV vaccination and screening for high-burden malignancies such as cervical cancer and Kaposi sarcoma. Screening protocols must be simple, cost-effective, and tailored to regional cancer profiles, which are characterised by earlier onset and greater aggressiveness in resource-limited settings.

A dedicated research agenda is essential to address unique drivers of cancer in African populations. Priorities include investigating viral and host genetics, characterising the tumour microenvironment, evaluating practical point-of-care diagnostics, and understanding how endemic co-infections and chronic immune activation amplify cancer risk. Enhanced cancer surveillance in people living with HIV is also critical to monitor trends and evaluate interventions.

Progress depends on addressing structural and social inequities. Strengthening health systems through decentralised services, improved diagnostics, and multidisciplinary teams is crucial,

alongside tackling stigma, poverty, and gender inequality through community engagement and equitable policies.

Healthy long-term outcomes must combine sustained virological control with lifelong cancer vigilance, supported by research into links between immune dysfunction, ageing, and carcinogenesis. Scaling this response will require regional collaboration, political commitment, and investment in surveillance systems and cancer registries. Aligning these efforts with global initiatives, such as the WHO's cervical cancer elimination strategy, will accelerate progress toward equitable cancer control for people living with HIV.

Author contributions

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Conflict of interest

The authors declare no conflict of interest.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study

Ethics statement

Not applicable.

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CHAPTER 3

Prevalence of HIV and associated risk factors among cancer patients in KwaZulu-Natal, South Africa

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Abstract

Introduction: HIV and cancer represent overlapping public health challenges in sub-Saharan Africa, particularly in South Africa, KwaZulu-Natal (KZN) province. While national data is available, detailed insights into the intersection of HIV and cancer within cancer populations in KZN remain limited.

Methods: A nested, cross-sectional study was conducted using data from 1,541 adult cancer patients enrolled in the Cancer Genetics Study (CGS) cohort at a tertiary hospital in Durban, KZN, between 1 June 2024 and 30 June 2025. HIV prevalence was calculated, and univariable logistic regression was used to assess associations between HIV status and specific cancer types. Multivariable logistic regression identified demographic and clinical factors associated with AIDS-defining cancers (ADCs).

Results: HIV prevalence among cancer patients was 34.8%, which is more than twice the provincial rate (16%) and the national rate (17.2%) in the general population. All PLWH were receiving antiretroviral therapy (ART). Prevalence was higher among women (41.2%), Black African patients (44.7%), and those aged 39–48 years (59.6%). ADCs accounted for 55.4% of malignancies, while NADCs accounted for 44.6%. Vulval (93.2%), anal (72.2%), and cervical (57.1%) cancers were more common among PLWH. Univariable analysis showed increased odds of HIV infection among patients with HPV-related malignancies, specifically for vulval (OR = 25.97; 95% CI: 7.21–127.40; p<0.001), anal (OR = 4.94; 95% CI: 1.43–19.32 p=0.0148), and cervical (OR = 2.53; 95% CI: 1.16–5.84; p=0.0224) cancers. A lower proportion of patients with leukaemia were HIV-positive (1.6%; OR = 0.28; 95% CI: 0.12–0.69; p=0.0042), with no significant association for breast cancer (OR = 1.08; 95% CI: 0.50–2.48; p=0.8566). Multivariable logistic regression, adjusted for age, gender, and race, identified HIV-positive status (adjusted OR =2.58; 95% CI:1.76–3.83; p<0.001), female sex (adjusted OR =18.62;95% CI: 9.95–39.75; p<0.001), and older age were all independently associated with a diagnosis of an AIDS-defining cancer.

Conclusions: HIV prevalence among cancer patients in KwaZulu-Natal remains high despite universal ART coverage. Strong associations with HPV-related malignancies persist, underscoring the need for integrated care. These findings support the integration of HIV and oncology services, including targeted screening and HPV vaccination, to address the dual burden of disease.

Keywords: HIV, cancer, KwaZulu-Natal, Epidemiology, HPV

Introduction

The syndemic of HIV and cancer presents a critical public health challenge in sub-Saharan Africa. In 2024, an estimated 40.8 million people were living with HIV globally (1). Women and girls remain disproportionately affected, accounting for 53% of people living with HIV and nearly 63% of new infections in sub-Saharan Africa (1). South Africa remains the epicentre of the epidemic, with approximately 7.8 million people living with HIV (PLWH) and 17.2% of HIV prevalence (2). Within the country, KwaZulu-Natal (KZN) is the most affected province, with an adult HIV prevalence of 16.0% in 2022 (3).

The widespread rollout of antiretroviral therapy (ART) has reduced HIV-related morbidity and mortality, transforming HIV from a fatal disease into a manageable chronic condition (4). Despite immune reconstitution from ART, PLWH face a rising burden of age-related comorbidities, particularly cancer (5). PLWH remain at an elevated risk for malignancies due to persistent immune dysfunction, oncogenic viral coinfections such as human papillomavirus (HPV), Epstein–Barr virus (EBV), and human herpesvirus 8 (HHV-8), as well as chronic inflammation and metabolic complications associated with long-term ART use (6-8). In addition, HIV-encoded proteins (Tat, Nef, Vpr) exert direct oncogenic effects by promoting genomic instability, while impaired immune surveillance enhances the oncogenic potential of coinfecting viruses (9, 10).

HIV-associated cancers are classified into two groups. AIDS-defining cancers (ADCs) include Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer. Non-AIDS-defining cancers (NADCs) include a wider range of malignancies, such as lung, liver, colorectal, breast, and prostate cancers. Epidemiological trends indicate a shift from ADCs to NADCs among aged PLWH in high-income settings, driven by longer survival, prolonged immunosuppression, and lifestyle factors (11, 12). However, in sub-Saharan Africa, ADCs remain disproportionately prevalent. The South African HIV Cancer Match Study (2004–2014) reported cervical cancer (27.5%) and KS (15.0%) as the most common malignancies among PLWH, with risks strongly dependent on CD4 counts (13). Young adults and adolescents living with HIV remain particularly vulnerable, experiencing significantly higher risks of KS and cervical cancer (14).

A recent meta-analysis confirmed that HIV coinfection more than doubles the risk of cervical cancer in Southern Africa, mainly due to impaired clearance of high-risk HPV. At the same time, higher CD4 counts (>500 cells/μL) confer significant protection (15, 16). Yet despite

these insights, important data gaps persist. For example, only 22% of cancer records in Malawi (2018–2019) documented HIV status, compared to 86–92% in Zimbabwe and South Africa (17). Furthermore, recent, site-specific data describing the burden of HIV-associated cancers in KZN remain limited (13) (18).

This study, therefore, aimed to fill the knowledge gaps and determine the prevalence of HIV and its associated risk factors among cancer patients in the KwaZulu-Natal province, to inform and guide the implementation of integrated HIV-oncology care services.

Methods

Study Design and eligibility criteria

This was a nested cross-sectional study using data collected between 1 June 2024 to 1 June 2025. Cancer-related data were obtained from the Cancer Genetics Study (CGS) cohort, which collected epidemiological data and biological specimens, including tissue and blood samples for genetic analysis in South African populations. All 1541 participants were recruited from Inkosi Albert Luthuli Central Hospital (IALCH), a tertiary referral hospital located in Durban, KwaZulu-Natal.

We included adult cancer patients of African descent. Eligible participants had a histologically confirmed cancer diagnosis, were aged 18 years or older at the time of recruitment and were permanent residents of KwaZulu-Natal. Only patients who had provided written informed consent for participation in the CGS cohort were included. Patients who did not meet these criteria were excluded. Ethical approval for this study was obtained from the Biomedical Research Ethics Committee (BREC) at the University of KwaZulu-Natal (protocol number BREC/00008300/2025). All participants had previously provided written informed consent for the use of their data in research conducted under the Cancer Genetics Study (CGS) cohort.

Data collection

Data was extracted from interviewer-administered questionnaires. Variables captured for this study included demographic characteristics (age, sex, race, and residential address), behavioural factors (smoking status and alcohol consumption), and reproductive health indicators for female participants (use of hormonal contraceptives). Clinical variables included height, weight, body mass index (BMI), blood group, rhesus factor, and chronic comorbidities, including HIV infection (self-reported), diabetes, and hypertension. Cancer-related information included anatomical site, cancer type, clinical stage, date of diagnosis, and treatment history. Data on medication use included antiretroviral therapy and other long-term

medications. Family history of cancer and the availability of biological specimens, including tissue and blood samples for future genetic analysis, were also recorded.

Sampling strategy and sample size determination

An a priori sample size calculation was based on an expected HIV prevalence of 32.6% among cancer patients in South Africa, as reported by Dhokotera et al (18). Using a 95% confidence level and a 5% margin of error, the minimum required sample size was estimated at 338 participants. The analysis included the entire CGS cohort recruited during the study period to maximise statistical power and precision for subgroup analyses. After data cleaning, which involved removing incomplete demographic or clinical information and duplicate entries, the final analytical sample comprised 1,541 patients.

Statistical Analysis

All statistical analyses were conducted using R version 4.3.3. Descriptive statistics were generated for all variables. Group comparisons by HIV status were performed using Pearson's chi-squared test or Fisher's exact test, as appropriate.

Univariable logistic regression was used to assess associations between HIV status and each specific cancer type, with Hodgkin lymphoma as the reference category (Supplementary Table 1, Figure 3).

Multivariable logistic regression was then performed to identify factors independently associated with a diagnosis of an AIDS-defining cancer (ADC). The model was adjusted for a priori confounders, including age, gender, and race. Results are reported as adjusted odds ratios (aORs) with 95% confidence intervals (CIs) (Supplementary Table 2, Figure 4).

Categorical variables were treated as factors with predefined reference groups. A p-value of < 0.05 was considered statistically significant.

Results

In this section, we first present descriptive statistics and univariable analyses examining associations between HIV status and cancer types (Supplementary Table 1, Figure 3). We then present multivariable logistic regression analyses, adjusted for age, gender, and race, to identify factors independently associated with AIDS-defining cancers (Supplementary Table 2, Figure 4)

Prevalence and Sociodemographic Associations

This nested cross-sectional study included 1,541 individuals. The overall HIV prevalence was 34.8% with all HIV-positive patients receiving antiretroviral therapy. HIV prevalence varied significantly across age groups. The highest proportions of HIV-positive individuals were observed in the 39–48-year (59.6%), followed by the 29–38-year group (49.3%) and the 49–58-year (45.3%) group. Lower prevalence was observed in the youngest (18–28 years; 11.8%) and oldest (≥65 years; 7.0%) age groups. Marked disparities were observed by race ($p < 0.001$). HIV positivity was highest among Black participants, 44.7%. In contrast, no White participants were HIV-positive 0%, and prevalence was low among Indian 1.2% and Coloured 5.1% participants. A significant association was also found with gender, with a higher prevalence among female participants (41.2%) than among males (20.4%; $p<0.001$). HIV prevalence was significantly higher in patients with AIDS-defining cancers, 55.4%, than in those with non-AIDS-defining cancers, 29.1% ($p<0.001$). No significant associations were found between HIV status and alcohol use ($p=0.247$) or smoking status ($p=0.160$). A small, but significant difference, was observed in family history of cancer; patients with a family history had a lower prevalence of HIV, 30.7% than those without 36.3%, ($p=0.046$). Non-HIV comorbidities were significantly less common in HIV-positive patients ($p<0.001$) (Table 1).

Table 1. Sociodemographic and clinical characteristics of the study population by HIV status (N=1,541)

Variable	Level	Total	HIV Positive (n, %)	HIV Negative (n, %)	P-value
Age Group (years)	18-28	119	14 (11.8%)	105 (88.2%)	-
	29-38	213	105 (49.3%)	108 (50.7%)	<0.001
	39-48	327	195 (59.6%)	132 (40.4%)	<0.001
	49-58	329	149 (45.3%)	180 (54.7%)	<0.001
	59-65	252	52 (20.6%)	200 (79.4%)	0.042

	65+	301	21 (7%)	280 (93%)	0.119
Race	White	68	0 (0%)	68 (100%)	-
	Black	1,188	531 (44.7%)	657 (55.3%)	<0.001
	Indian	246	3 (1.2%)	243 (98.8%)	<0.001
	Coloured	39	2 (5.1%)	37 (94.9%)	<0.001
Gender	Male	476	97 (20.4%)	379 (79.6%)	-
	Female	1,065	439 (41.2%)	626 (58.8%)	<0.001
Type of cancer	Non-AIDS-defining	1,209	352 (29.1%)	857 (70.9%)	-
	AIDS-defining	332	184 (55.4%)	148 (44.6%)	<0.001
Alcohol Use	No	1,434	493 (34.4%)	941 (65.6%)	-
	Yes	107	43 (40.2%)	64 (59.8%)	0.247
Smoking status	No	1,404	496 (35.3%)	908 (64.7%)	-
	Yes	137	40 (29.2%)	97 (70.8%)	0.160
History of Cancer in the family	No	1,131	410 (36.3%)	721 (63.7%)	-
	Yes	410	126 (30.7%)	284 (69.3%)	0.046
Comorbidities (excl. HIV)	No	905	380 (41.9%)	525 (58%)	-

	Yes	636	156 (24.5%)	480 (75.5%)	<0.001

Table 2. Comparison of HIV characteristics: Current Cancer Cohort vs National Estimates

Variable	Current Study (Cancer Patients)	National Estimates (General Population)
HIV Prevalence	34.8%	17.2%
ART Coverage	100%	81%
Women Living With HIV	41.2%	23%
Men Living With HIV	20.4%	11.3%

The current study reflects HIV characteristics among oncology patients, whereas national estimates represent the general population irrespective of cancer status (2).

Distribution of Cancer Types by HIV Status

HIV burden varied across cancer types. (Figure 1). The most common malignancies among all patients were breast cancer 23.0%, cervical cancer 20.4%, and leukaemia 12.7% (Figure 1). The prevalence of HIV exceeded 50% among patients with vulval 93.2%, anal 72.2%, and cervical 57.1% cancers. Conversely, several cancer types, including ovarian, endometrial, and testicular cancers, had very few or no HIV-positive cases. This distribution underscores the significant overlap between HIV and specific virus-associated malignancies. The complete analysis can be found in the Supplementary (supplementary table 2)

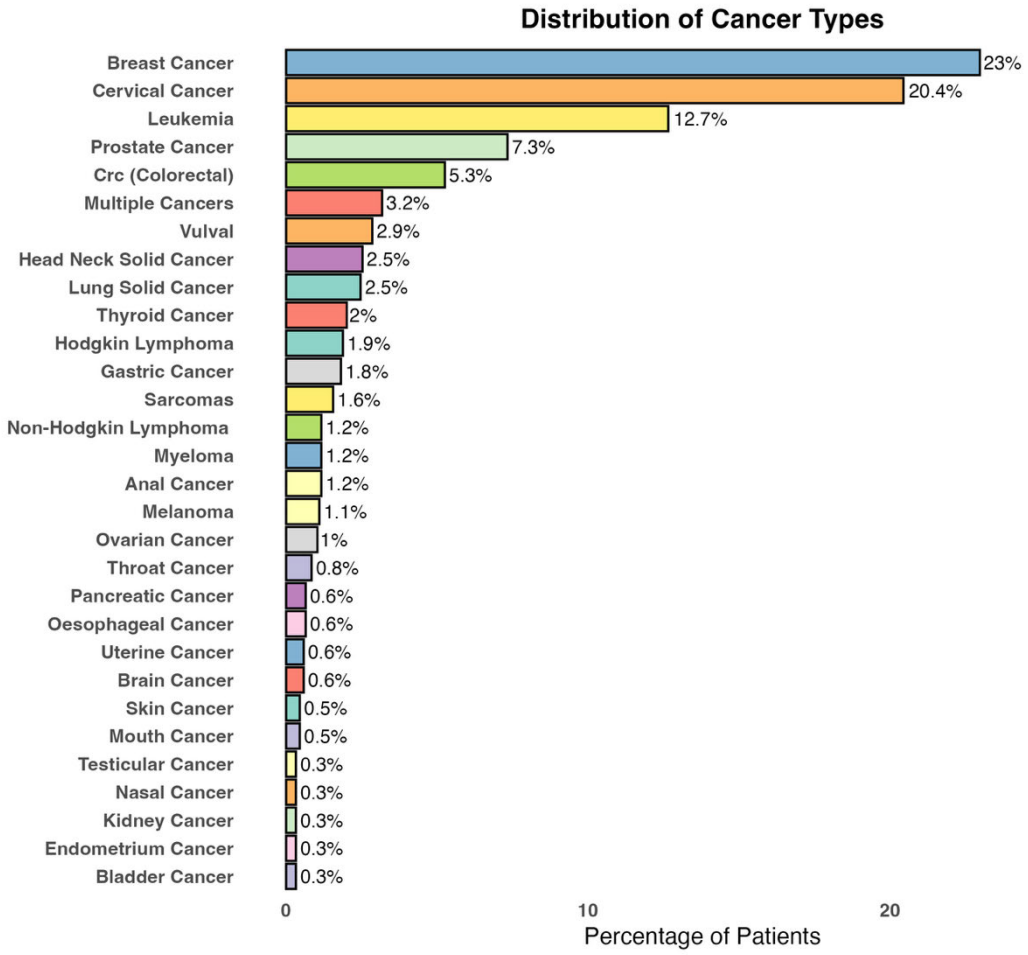

Figure 1: Distribution of Cancer Types. Overall distribution of cancer types among 1,541 patients in KwaZulu-Natal. Each bar represents the percentage of a specific cancer type within the study population.

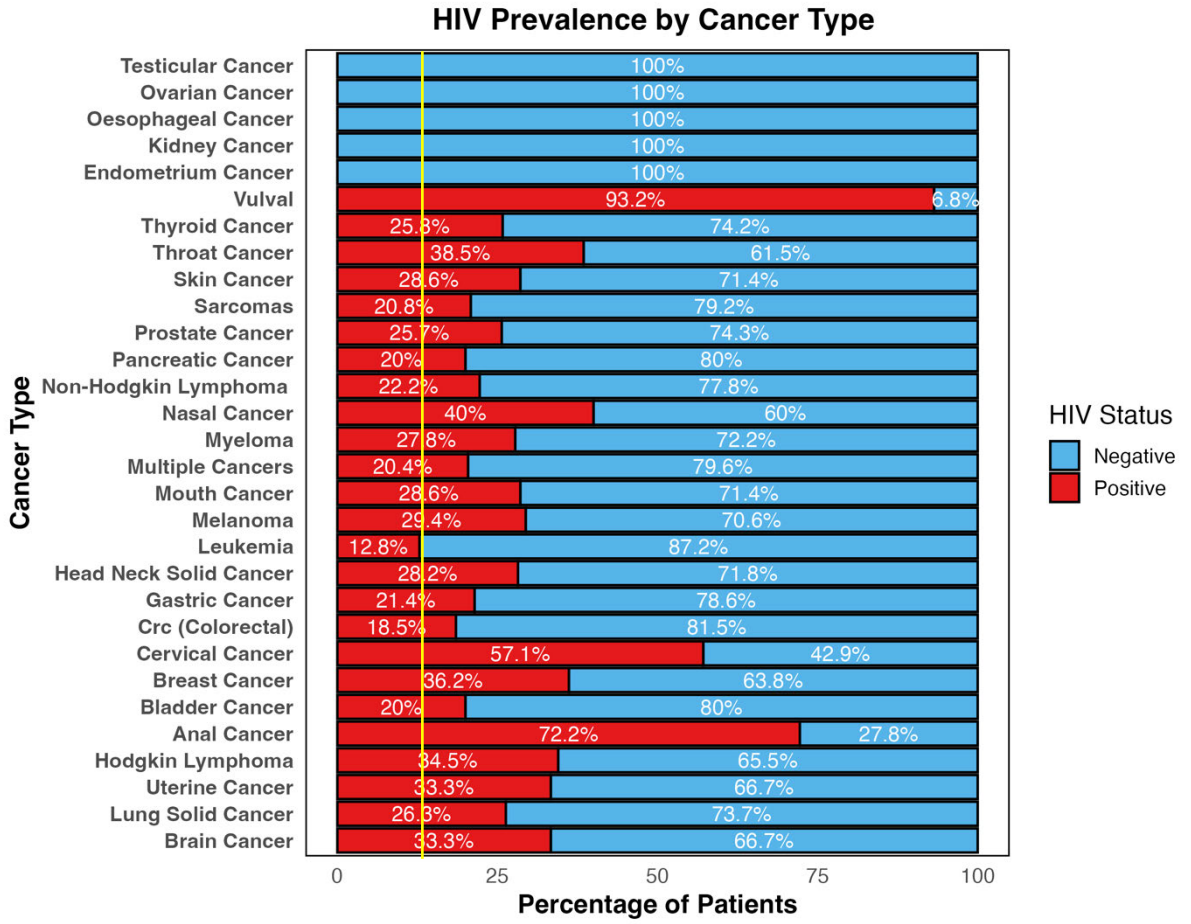

Figure 2: HIV Prevalence by Cancer Type. Distribution of cancer types among 1,541 patients in KwaZulu-Natal, stratified by HIV status. Marked differences in cancer type prevalence were observed between HIV-positive and HIV-negative individuals. The yellow reference line represents the estimated HIV prevalence in the general KwaZulu-Natal population (16%), independent of cancer diagnosis.

Association between HIV Status and Specific Cancer Types

Univariable logistic regression analysis revealed significant associations between HIV status and specific cancer types (Figure 2). HPV-related malignancies showed the strongest associations with HIV positivity, with vulval cancer presenting the highest odds (OR = 25.97; 95% CI: 7.21–127.40; $p < 0.001$) and anal cancer also significantly associated (OR = 4.94; 95% CI: 1.43–19.32; $p = 0.015$). Cervical cancer was also associated with increased odds of HIV infection (OR = 2.53; 95% CI: 1.16–5.84; $p = 0.022$). In contrast, leukaemia was associated with lower odds of HIV infection (OR = 0.28; 95% CI: 0.12–0.69; $p = 0.004$). No statistically significant associations were observed for other malignancies. Point estimates for

prostate (OR = 0.66; 95% CI: 0.25–1.75), colorectal (OR = 0.43; 95% CI: 0.10–1.85), lung (OR = 0.68; 95% CI: 0.18–2.50), breast (OR = 1.08; 95% CI: 0.50–2.48), and throat cancers (OR = 1.19; 95% CI: 0.30–4.70) were also reported, though these did not reach statistical significance. The complete analysis can be found in the Supplementary (supplementary table 1)

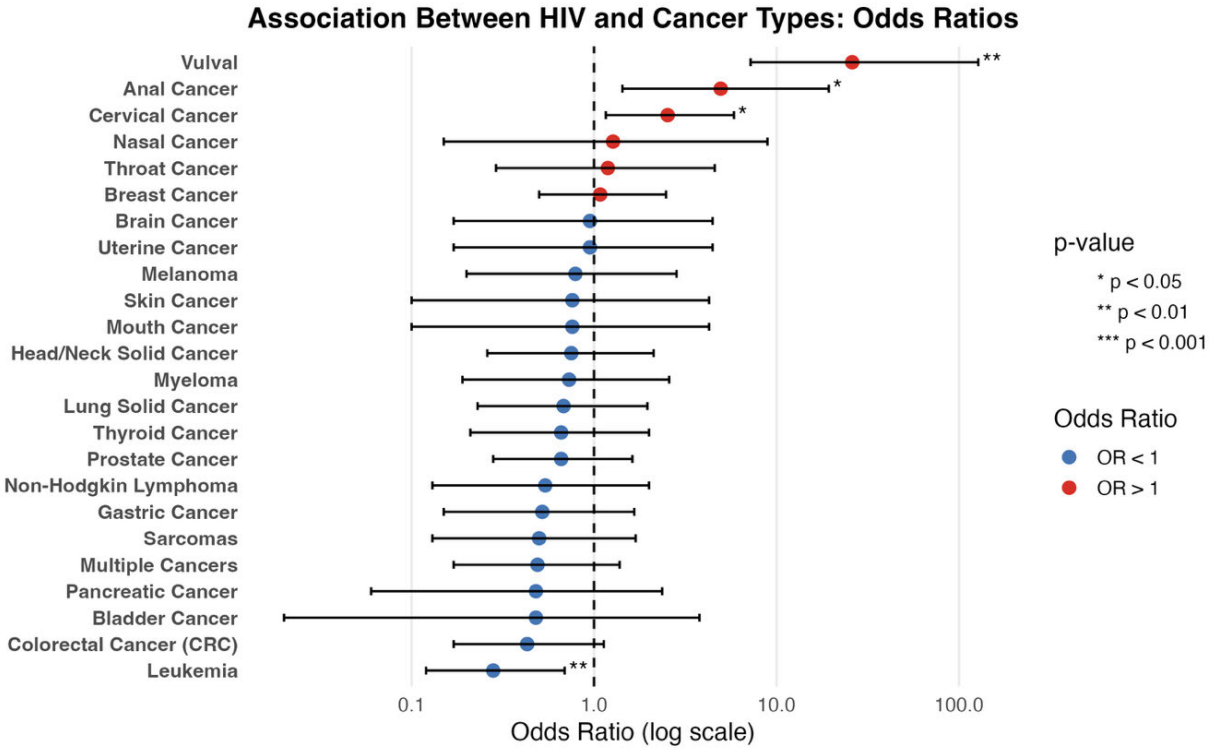

Figure 3: Univariable analysis – Association between HIV status and specific cancer types. Association between HIV status and specific cancer types among 1,541 patients in KwaZulu-Natal. The forest plot displays odds ratios (OR) with 95% confidence intervals for each cancer type, comparing HIV-positive to HIV-negative individuals. The vertical dashed line at OR = 1 denotes no association. Red markers indicate cancers with higher odds among HIV-positive patients (OR > 1), while blue markers indicate cancers with lower odds (OR < 1). Hodgkin lymphoma was used as the reference category. Statistical significance is indicated by asterisks (*p < 0.05, **p < 0.01, *** p < 0.001).

Risk Factors for AIDS-Defining Cancers (ADCs)

Multivariable analysis was conducted to identify factors independently associated with a diagnosis of an AIDS-defining cancer (ADC) (Figure 3). In multivariable analysis adjusted for age, gender, and race, HIV status (adjusted odds ratio 2.58; 95% CI 1.76 to 3.83; P<0.001) and female sex (adjusted odds ratio 18.62; 95% CI 9.95 to 39.75; P<0.001) were the strongest

predictors of an ADC diagnosis. Patients in older age groups also had significantly higher odds of an ADC compared to the youngest patients, with adjusted odds ratios ranging from 2.32 (age 39–48) to 3.08 (age 59–65). The presence of other comorbidities was associated with significantly higher odds of an AIDS-defining cancer (aOR = 1.73; 95% CI: 1.14-2.64; p = 0.011), suggesting that additional chronic conditions may contribute to cancer risk in this population. Behavioural factors such as smoking and alcohol use showed no significant associations in the adjusted model. Full results are presented in Supplementary Table 3

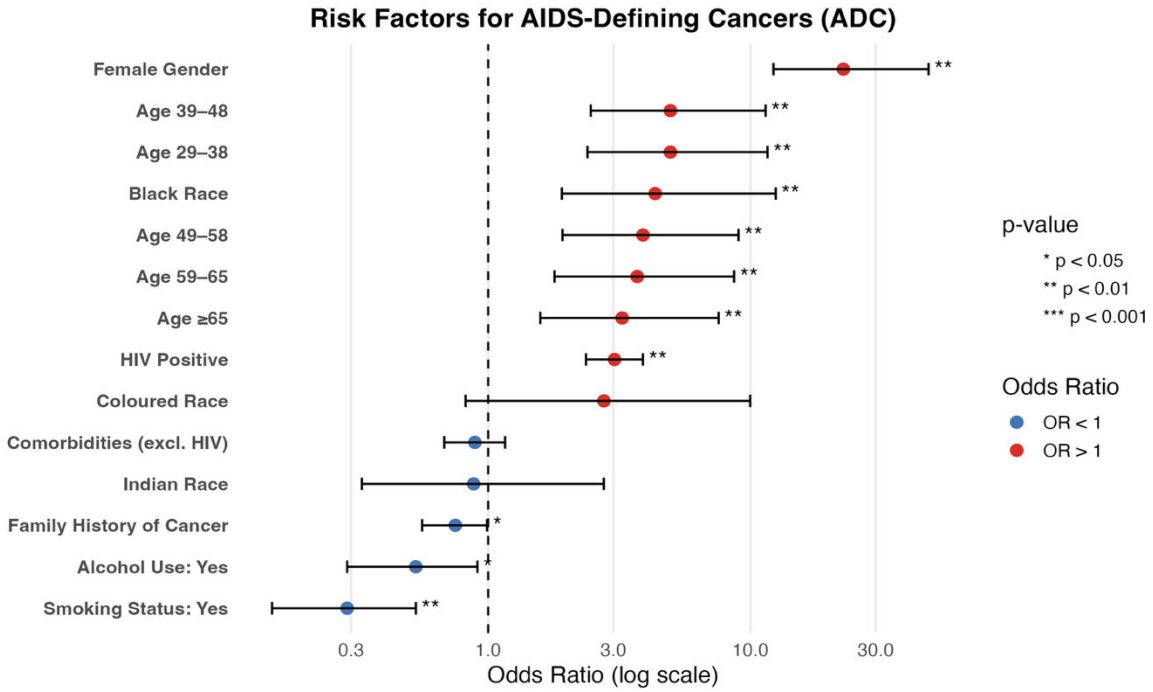

Figure 4:Multivariable analysis – Risk factors for AIDS-defining cancers (adjusted for age, gender, and race)

Risk factors for AIDS-defining cancers (ADCs) among 1,541 patients in KwaZulu-Natal. The forest plot presents adjusted odds ratios (aORs) with 95% confidence intervals for variables included in the multivariate logistic regression model, adjusted by age, gender and race. The vertical dashed line at aOR = 1 denotes no association. Red markers indicate factors associated with increased odds of ADC diagnosis (aOR > 1), while blue markers indicate factors associated with decreased odds (aOR < 1). Reference categories: Age 18–28 years, Black race, and male gender. Statistical significance is indicated by asterisks (*p < 0.05, **p < 0.01, *** p < 0.001).

Discussion

This nested cross-sectional study of 1,541 cancer patients highlights a disproportionate burden of HIV within the cancer population. If HIV did not influence cancer risk, the prevalence among cancer patients would be similar to the national average of 17.2%. However, the observed prevalence was 34.8%, nearly double the national figure, indicating a strong association between HIV and cancer in this setting. ART coverage was universal (100% compared with 81% nationally), and the proportion of women living with HIV was almost double (41.2% compared with 23% nationally). HIV prevalence was particularly high among younger cancer patients, especially those aged 39–48 years (59.6%), pointing to a critical demographic shift. Among people living with HIV, 55.4% had AIDS-defining cancers. These findings indicate that, even with widespread ART coverage, HIV-associated cancers remain common. (Table1and 2).

Our results are broadly consistent with regional and national evidence, reinforcing the high burden of HIV among cancer patients in southern Africa. The overall prevalence of 34.8% exceeds the 33.7% reported from Johannesburg a decade ago (19) and is more than three times higher than the 10.6% recently documented in a Kenyan tertiary hospital (20). Our findings align with a national record linkage study in South Africa, which found that 50% of female cancer patients in the public sector with a known HIV status were HIV-positive (21). These results contribute to an evolving narrative documented by the Johannesburg Cancer Study, which over 22 years has demonstrated a shifting burden of HIV-associated cancers in South Africa, with risks for many virus-related malignancies remaining elevated in the ART era (13). This regional burden is further supported by a recent global study, which estimated that 70.5% of all HIV-attributable cancers worldwide occur in Africa, with Southern Africa bearing the highest age-standardised incidence rate in the world at 27.6 per 100,000 (22). Importantly, our findings are contextualised by a 30-year national analysis from Botswana, which found that 49.5% of all cancer cases occurred in PLWH (23). These results indicate that South Africa remains a region with a severe HIV–cancer syndemic. Importantly, our near-complete ascertainment of HIV status addresses the under-reporting observed in some African cancer registries, such as Malawi, where only 22% of records included HIV status (17).

HIV-positive cancer patients presented at significantly younger ages, consistent with findings from the South African HIV Cancer Match study, which reported a median age of 33 years at cancer diagnosis among people living with HIV (24). This early onset of malignancy is likely influenced by HIV-related immunodeficiency, as demonstrated by a dose-response relationship between lower CD4 counts and higher incidence of infection-related cancers (25).

As highlighted in the literature review (Chapter 2), HPV-related malignancies are consistently elevated in HIV-positive populations due to immune suppression. Our findings confirm this pattern, with vulval, anal, and cervical cancer showing the strongest associations with HIV status.

At the cancer-specific level, our findings are consistent with international evidence on HIV-associated cancer risk. The markedly elevated odds for HPV-related cancers in our study, vulval (OR = 25.97), anal (OR = 4.94), and cervical (OR = 2.53), mirror patterns reported in other high HIV-prevalence settings. For example, Hernández-Ramírez et al. documented substantially increased incidence of anal cancer (SIR = 19.1) and cervical cancer (SIR = 3.24) among HIV-infected individuals in the United States (26). Although our study estimated HIV prevalence among cancer patients, whereas these studies assessed cancer incidence in HIV-positive populations, the convergence across different designs supports the hypothesis that HIV-related immunosuppression contributes to HPV-driven oncogenesis. National data further support this association. The South African National Cancer Registry (2011–2021) reported persistently high cervical cancer incidence (30.4 cases per 100,000 person-years) and rising rates of vulvar, vaginal, penile, and anal squamous cell carcinomas, particularly among Black individuals and younger women (27). These trends highlight the growing burden of HPV-related malignancies in South Africa and the amplifying effect of HIV coinfection. Globally, anal cancer remains disproportionately concentrated among people living with HIV, with prevalence exceeding 40% among anal cancer patients in high HIV-prevalence regions such as Africa (28). A recent study from Ghana further supports this link, reporting hrHPV prevalence of 44.4% among women living with HIV and a positive association between longer HIV duration and infection risk (29).

Univariable analysis showed a non-significant inverse association between prostate cancer and HIV infection (OR = 0.66; 95% CI: 0.28–1.62; p = 0.345) (Figure 3). This trend is broadly consistent with findings from high-income countries, where studies often report a null or modestly reduced risk of prostate cancer among people living with HIV. For example, the US HIV/AIDS Cancer Match Study reported a 50% reduction in prostate cancer risk (SIR = 0.48) (26), and a systematic review and meta-analysis by Sun et al., pooling 27 cohort studies, found a significantly lower incidence (SIR = 0.76; 95% CI: 0.64–0.91; p = 0.003) (30). However, while these international studies suggest a protective effect, our findings did not reach statistical significance. Several mechanisms may contribute to the lower incidence of prostate cancer among men living with HIV. Testosterone deficiency is reported in roughly 34.5% of

HIV-positive men and occurs at younger ages due to chronic inflammation and immune dysregulation, which may reduce androgen-driven tumour development (31). Additionally, preclinical evidence suggests that specific antiretroviral agents, particularly protease inhibitors, exert anti-proliferative effects on prostate cancer cells, potentially influencing cancer risk (30). However, the relationship is complex and may also be influenced by healthcare factors. This inverse association may reflect differences in screening and diagnosis rather than true variation in biological risk. A plausible explanation for the apparent lower risk is screening bias. People living with HIV may undergo less frequent PSA testing due to competing clinical priorities, leading to underdiagnosis. This interpretation is supported by South African data showing that the reduced incidence disappears after adjusting for PSA testing and biopsy rates (32). In contrast, a large population-based study in Soweto reported a higher prevalence of HIV among men with prostate cancer compared to controls, suggesting that regional differences in screening practices and HIV epidemiology may shape observed associations. These contrasting findings underscore the need for context-specific research in African populations.

A similar pattern was observed for breast cancer; women with HIV had slightly higher odds in univariable analysis (OR = 1.08; 95% CI: 0.50–2.48; p = 0.8566), though not statistically significant. International studies report lower risk, including a 37% reduction in the United States (33). A proposed biological mechanism involves HIV strains using the CXCR4 co-receptor, which can bind to receptors on breast cells and trigger apoptosis of pre-malignant cells (34). Importantly, breast and prostate cancer represent distinct exceptions to the general pattern of increased cancer risk among PLWH.

Clinical and Policy Implications

These findings underscore the necessity of routine, opt-out HIV testing for cancer patients, which could improve early diagnosis and treatment in this setting. Integrating HIV and oncology services may enhance timely ART initiation and screening for virus-related cancers. Strengthening care models, supported by linked HIV cancer data systems, can guide long-term monitoring. Implementation studies should also assess the feasibility and cost-effectiveness of bundled screening, like HPV, PSA and breast ultrasound within HIV programs.

Strengths and Limitations

This study has several notable strengths. The large sample size, near-complete ascertainment of HIV status, and detailed site-specific cancer classification enhance the reliability of the

findings and strengthen internal validity. These features allow for a more robust examination of patterns across diverse cancer types within the study population.

However, several limitations should be acknowledged. First, the cross-sectional design precludes causal inference and limits the ability to determine temporal relationships between HIV infection and cancer diagnosis. Second, because the study was hospital-based and conducted at a tertiary referral centre, the findings may be subject to referral bias and may not be fully generalisable to all cancer patients in KwaZulu-Natal, particularly those managed in primary or secondary care settings.

Third, the use of secondary clinical data from the parent Cancer Genetics Study restricted the availability of key variables. Information on ART regimen type, duration, adherence, longitudinal CD4 trajectories, viral load suppression, and cancer staging was not available. The absence of these data limited our ability to assess the severity of immunosuppression, treatment-specific effects, or stage at presentation. Additionally, data on other oncogenic viral coinfections were not captured and therefore could not be examined.

Future Directions

Future research should focus on linking cancer registries with HIV clinical datasets to enable longitudinal analysis of interactions between immunosuppression, antiretroviral therapy use, and cancer development. Implementation studies are needed to assess the feasibility and cost-effectiveness of integrated screening bundles, including HPV testing, prostate-specific antigen (PSA) screening, and portable breast ultrasound, within existing HIV care platforms. In addition, molecular and genetic studies may help clarify biological mechanisms underlying cancer risk in people living with HIV. Host genetic factors, including HLA class II alleles associated with cervical cancer risk in South African women (35), warrant further investigation in the KZN population.

Conclusions

This study provides a regional assessment of cancer patterns among individuals living with HIV in KwaZulu-Natal. The findings confirm a high HIV prevalence among cancer patients and demonstrate strong associations with virus-related malignancies. Cancer patients represent a key population for HIV testing and linkage to care. Integrating HIV services with oncology care, including timely ART initiation and targeted cancer screening, may contribute to improved outcomes and reduced cancer burden in this population.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contributions

J.A.: Conceptualisation, Methodology, Formal Analysis, Investigation, Data Curation, Writing – Original Draft, Writing Review & Editing, Visualisation.

N.F.M.: Writing, Review & Editing, Visualisation.

A.G.: Writing, Review &Editing.

VR: Conceptualisation, Methodology, Resources, Writing, Review & Editing, Supervision, Funding Acquisition.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

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SUPPLEMENTARY

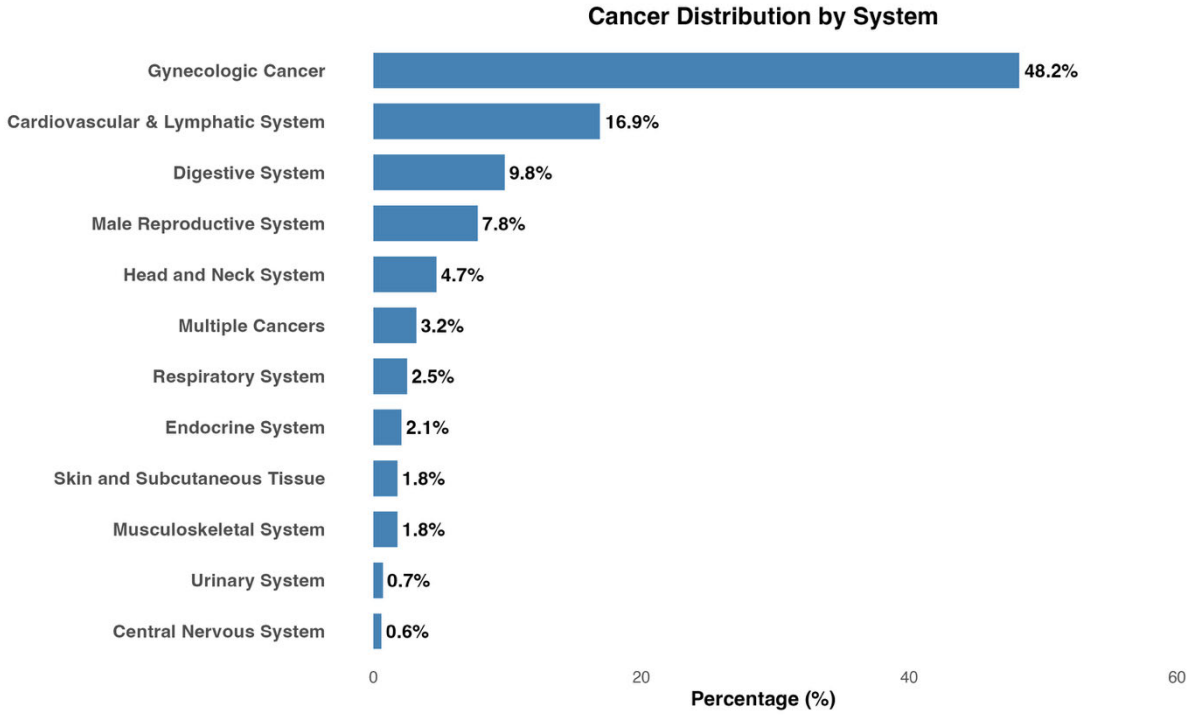
Supplementary Table 1: Cancer Type Frequencies by HIV Status and Univariable analysis (n = 1,541)

Cancer Type	**HIV Positive n (%)**	**HIV Negative n (%)**	**Total n (%)**	**Univ. OR (95% CI)**	**p-value**
Vulval	41 (2.7%)	3 (0.2%)	44 (2.9%)	25.97 (7.21–127.40)	<0.001
Prostate Cancer	29 (1.9%)	84 (5.5%)	113 (7.3%)	0.66 (0.28–1.62)	0.3446
Anal Cancer	13 (0.8%)	5 (0.3%)	18 (1.2%)	4.94 (1.43–19.32)	0.0148
Leukaemia	25 (1.6%)	170 (11.0%)	195 (12.7%)	0.28 (0.12–0.69)	0.0042
Cervical Cancer	180 (11.7%)	135 (8.8%)	315 (20.4%)	2.53 (1.16–5.84)	0.0224
Hodgkin Lymphoma	10 (0.6%)	19 (1.2%)	29 (1.9%)	–	–
Bladder Cancer	1 (0.1%)	4 (0.3%)	5 (0.3%)	0.48 (0.02–3.78)	0.5296
Bone Cancer	2 (0.1%)	1 (0.1%)	3 (0.2%)	–	–
Brain Cancer	3 (0.2%)	6 (0.4%)	9 (0.6%)	0.95 (0.17–4.46)	0.9494
Breast Cancer	128 (8.3%)	226 (14.7%)	354 (23.0%)	1.08 (0.50–2.48)	0.8566
CRC (Colorectal Cancer)	15 (1.0%)	66 (4.3%)	81 (5.3%)	0.43 (0.17–1.13)	0.0829
Endocrine Cancer	0 (0.0%)	1 (0.1%)	1 (0.1%)	–	–
Endometrium Cancer	0 (0.0%)	5 (0.3%)	5 (0.3%)	–	–
Eye Cancer	1 (0.1%)	0 (0.0%)	1 (0.1%)	–	–
Gastric Cancer	6 (0.4%)	22 (1.4%)	28 (1.8%)	0.52 (0.15–1.66)	0.2764
Head/Neck Solid Cancer	11 (0.7%)	28 (1.8%)	39 (2.5%)	0.75 (0.26–2.12)	0.5800
Kidney Cancer	0 (0.0%)	5 (0.3%)	5 (0.3%)	–	–
Liver Cancer	1 (0.1%)	2 (0.1%)	3 (0.2%)	–	–
Lung Solid Cancer	10 (0.6%)	28 (1.8%)	38 (2.5%)	0.68 (0.23–1.96)	0.4702
Maxillary Cancer	1 (0.1%)	0 (0.0%)	1 (0.1%)	–	–

Melanoma	5 (0.3%)	12 (0.8%)	17 (1.1%)	0.79 (0.20–2.83)	0.7235
Mouth Cancer	2 (0.1%)	5 (0.3%)	7 (0.5%)	0.76 (0.10–4.27)	0.7663
Multiple Cancers	10 (0.6%)	39 (2.5%)	49 (3.2%)	0.49 (0.17–1.38)	0.1728
Myeloma	5 (0.3%)	13 (0.8%)	18 (1.2%)	0.73 (0.19–2.58)	0.6322
Nasal Cancer	2 (0.1%)	3 (0.2%)	5 (0.3%)	1.27 (0.15–8.91)	0.8118
Nasopharyngeal Cancer	0 (0.0%)	1 (0.1%)	1 (0.1%)	–	–
Non-Hodgkin Lymphoma	4 (0.3%)	14 (0.9%)	18 (1.2%)	0.54 (0.13–2.00)	0.3749
Oesophageal Cancer	0 (0.0%)	10 (0.6%)	10 (0.6%)	–	–
Orbital Cancer	1 (0.1%)	0 (0.0%)	1 (0.1%)	–	–
Ovarian Cancer	0 (0.0%)	16 (1.0%)	16 (1.0%)	–	–
Palate Cancer	0 (0.0%)	2 (0.1%)	2 (0.1%)	–	–
Pancreatic Cancer	2 (0.1%)	8 (0.5%)	10 (0.6%)	0.48 (0.06–2.36)	0.3986
Pelvic Cancer	1 (0.1%)	0 (0.0%)	1 (0.1%)	–	–
Penile Cancer	1 (0.1%)	1 (0.1%)	2 (0.1%)	–	–
Peri-Anal Cancer	1 (0.1%)	0 (0.0%)	1 (0.1%)	–	–
Pituitary Gland Cancer	0 (0.0%)	1 (0.1%)	1 (0.1%)	–	–
Sarcomas	5 (0.3%)	19 (1.2%)	24 (1.6%)	0.50 (0.13–1.69)	0.2762
Skin Cancer	2 (0.1%)	5 (0.3%)	7 (0.5%)	0.76 (0.10–4.27)	0.7663
Spleen Cancer	0 (0.0%)	1 (0.1%)	1 (0.1%)	–	–
Squamous Cell Carcinoma	1 (0.1%)	2 (0.1%)	3 (0.2%)	–	–
Testicular Cancer	0 (0.0%)	5 (0.3%)	5 (0.3%)	–	–
Throat Cancer	5 (0.3%)	8 (0.5%)	13 (0.8%)	1.19 (0.29–4.58)	0.8036
Thyroid Cancer	8 (0.5%)	23 (1.5%)	31 (2.0%)	0.66 (0.21–2.00)	0.4648

Tongue Cancer	1 (0.1%)	0 (0.0%)	1 (0.1%)	–	–
Tracheal Cancer	0 (0.0%)	1 (0.1%)	1 (0.1%)	–	–
Uterine Cancer	3 (0.2%)	6 (0.4%)	9 (0.6%)	0.95 (0.17–4.46)	0.9494

Distribution of cancer types by HIV status and corresponding univariate logistic regression results among 1,541 patients in KwaZulu-Natal. The table presents the number and percentage of HIV-positive and HIV-negative patients diagnosed with each cancer type, along with univariate odds ratios (ORs) and 95% confidence intervals (CIs) estimating the association between HIV status and each cancer. P-values are reported for each test, with values < 0.05 considered statistically significant.



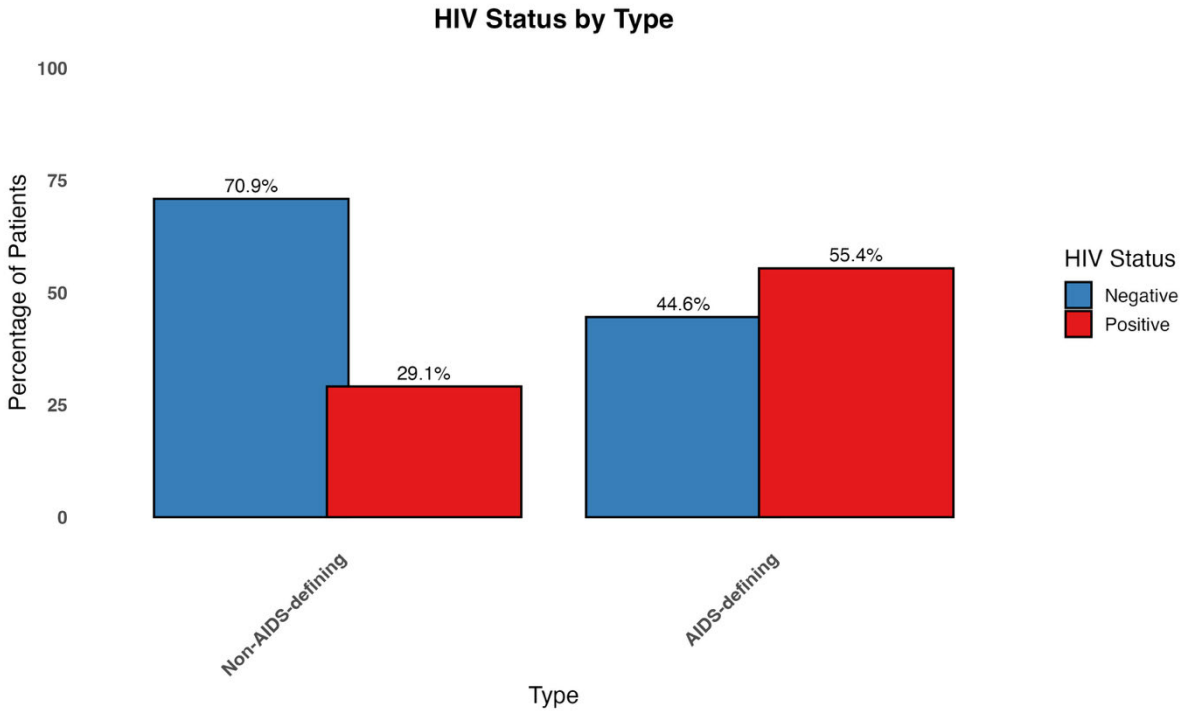
Supplementary Figure 1: Cancer Type distribution by system. HIV status distribution among patients with AIDS-defining and non-AIDS-defining cancers. The bar chart shows the percentage of HIV-positive and HIV-negative patients within each cancer category. Among AIDS-defining cancers, 55.4% of patients were HIV-positive compared to 44.6% HIV-negative, whereas for non-AIDS-defining cancers, 29.1% were HIV-positive and 70.9% HIV-negative.

Supplementary Table 2: Risk Factors Associated with AIDS-Defining

Variable	AIDS-Defining Cancers			
	Unadjusted OR (95% CI)	**p-value**	**Adjusted OR (95% CI)**	**p-value**
HIV Positive	3.03 (2.36–3.89)	<0.001	2.58 (1.76–3.83)	<0.001
Age 29–38	4.95 (2.39–11.61)	<0.001	2.47 (1.12–6.07)	0.034
Age 39–48	4.95 (2.46–11.42)	<0.001	2.32 (1.07–5.61)	0.043
Age 49–58	3.89 (1.92–9.00)	<0.001	2.17 (1.00–5.27)	0.064
Age 59–65	3.70 (1.79–8.66)	0.001	3.08 (1.38–7.63)	0.009
Age ≥65	3.24 (1.58–7.56)	0.003	2.89 (1.29–7.19)	0.014
Female Gender	22.59 (12.24–47.73)	<0.001	18.62 (9.95–39.75)	<0.001
Black Race	4.33 (1.91–12.48)	0.002	2.08 (0.83–6.36)	0.148
Coloured Race	2.76 (0.82–9.97)	0.104	1.32 (0.37–5.03)	0.671
Indian Race	0.88 (0.33–2.76)	0.804	0.58 (0.20–1.91)	0.332
Comorbidities (excl. HIV)	0.89 (0.68–1.16)	0.391	1.73 (1.14–2.64)	0.011
Smoking Status: Yes	0.29 (0.15–0.53)	<0.001	0.83 (0.39–1.65)	0.608
Alcohol Use: Yes	0.53 (0.29–0.91)	0.030	0.62 (0.31–1.14)	0.138
Family History of Cancer	0.75 (0.56–0.99)	0.045	0.74 (0.54–1.02)	0.070

Supplementary Table 2 Multivariable logistic regression – Adjusted odds ratios (aORs) for factors associated with AIDS-defining cancers, controlling for age, race, and gender (n = 1,541)

Estimates are adjusted for age, gender, and race. Reference categories: Age 18–28 years, Black race, and male gender. Statistical significance: *p < 0.05, **p < 0.01, ***p < 0.001.



Supplementary Figure 2: Distribution of HIV status across cancer category among 1,541 patients in KwaZulu-Natal. HIV positivity was markedly higher among AIDS-defining cancers (55.4%) compared to non-AIDS-defining cancers (29.1%).

CHAPTER IV. SYNTHESIS

The intersection of HIV and cancer in sub-Saharan Africa represents more than a simple comorbidity; it constitutes a syndemic, a synergistic interaction of multiple diseases compounded by social and structural inequities, resulting in an amplified burden of morbidity and mortality. This thesis, integrating a comprehensive literature review with epidemiological data, identifies SSA as a critical epicentre of this syndemic. The widespread scale-up of ART has transformed HIV into a chronic condition; however, this success has introduced a new challenge: the coexistence of persistent ADCs and an increasing incidence of NADCs.

The analysis presented here indicates that the HIV–cancer dynamic in KwaZulu-Natal is not a linear progression from one era to another but a simultaneous dual burden, resulting in a distinct KZN phenotype of malignancy. This phenotype reflects a combination of biological factors, such as oncogenic viruses and chronic immune dysregulation, as well as structural determinants, including diagnostic delays, healthcare inequities, and broader social determinants of health. Collectively, these findings provide an evidence-based rationale for reorienting public health strategies from disease-specific approaches toward integrated syndemic management.

The most compelling evidence of syndemic interaction in KwaZulu-Natal emerges from the disparity in HIV prevalence among cancer patients. Within this cohort of 1,541 individuals, 34.8% were living with HIV, a figure that far exceeds the national prevalence of approximately 17.2% and the provincial rate of 16.0% (4, 6). This near doubling of risk underscores HIV as a significant oncogenic factor; if HIV were not associated with cancer, prevalence within oncology units would approximate community levels. Instead, this disproportionate burden confirms HIV as a major risk determinant for malignancy in this setting.

This finding aligns with regional trends. A 30-year national analysis from Botswana reported that 49.5% of all cancer cases occurred among PLWH (26), suggesting that KwaZulu-Natal's experience is part of a broader Southern African crisis despite decades of ART rollout. Importantly, this elevated prevalence is not evenly distributed across all populations. Women (41.2%), Black African (44.7%), and individuals aged between 39–48 years (59.6%) bear the most significant burden. This demographic pattern reflects the intersection of biological susceptibility with persistent social and structural determinants, including gender inequities, economic disparities, and geographic barriers to care. The concentration of cases among younger adults challenges the conventional paradigm of cancer as a disease of ageing and signals accelerated carcinogenesis in the context of HIV.

HIV-associated cancer is primarily mediated by immunosuppression, which compromises immune surveillance of oncogenic viruses. Empirical data from KwaZulu-Natal corroborate this mechanism: ADCs accounted for 55.4% of malignancies among PLWH, with HPV-related cancers showing markedly elevated odds ratios. HIV co-infection was 26-fold higher in vulval cancer (OR = 25.97), five-fold higher in anal cancer (OR = 4.94), and 2.5-fold higher in cervical cancer (OR = 2.53). These associations represent the clinical impact of high-risk HPV and other oncogenic viruses in immunocompromised hosts. Comparable trends across SSA, such as reports that up to 75% of cervical cancer patients in Eswatini are HIV-positive, affirm (21) that KwaZulu-Natal is experiencing a concentrated manifestation of a regional challenge.

A critical insight emerging from this analysis is the ART paradox. In this cohort, 100% of HIV-positive cancer patients were receiving ART, a coverage rate surpassing the national average of 81% (4). Yet, this universal treatment coexists with a substantial burden of HIV-associated cancers. This paradox challenges the assumption that viral suppression alone mitigates cancer risk. Persistent immune dysregulation and chronic inflammation, characterised by elevated pro-inflammatory cytokines such as IL-6 and TNF-α, create a pro-tumour microenvironment conducive to cellular proliferation, angiogenesis, and genomic instability (11, 12). Thus, while ART remains indispensable for reducing certain ADCs, it provides only partial protection against long-term cancer risk, particularly for virally driven malignancies (27).

The emergence of NADCs, which now account for 29.1% of cancers in our HIV-positive cohort, reflects the success of ART in prolonging life for PLWH but introduces new clinical challenges. For many NADCs, the issue is not elevated incidence but poorer outcomes, driven by late-stage diagnosis and aggressive tumour biology. This dynamic is exemplified by prostate and breast cancer. The observed null association for prostate cancer (OR = 0.66) represents an epidemiological artefact rather than an actual protective effect. Evidence from South African cohort studies indicates that this apparent reduction disappears after adjusting for PSA testing and biopsy rates (28, 29). Men living with HIV are less likely to undergo routine PSA screening, likely due to competing clinical priorities within HIV care, resulting in underdiagnosis and more advanced disease at presentation.

Similarly, the overall null association for breast cancer (OR = 1.08) suggests a more concerning, subtype-specific reality. A recent South African study reported that while HIV was not associated with breast cancer overall, it was linked to a 39% increased odds of triple-negative breast cancer, a highly aggressive subtype with limited therapeutic options and poor survival outcomes (30). This suggests that HIV may not elevate the initial risk of breast cancer

but modifies its biological behaviour, potentially through chronic inflammation and immune dysregulation, promoting more lethal phenotypes. The inverse association observed for leukaemia (OR = 0.28) further underscores HIV's selective oncogenic influence, disproportionately amplifying cancers with strong infectious etiologies while exerting null or inverse effects on others.

Synthesising the literature with empirical data reveals a distinctive KZN phenotype of HIV-associated cancer, echoing the broader SSA phenotype described in regional studies. This phenotype is defined by an earlier age of onset, predominance of virally driven malignancies, and aggressive tumour histology. It reflects a synergistic interplay between biological vulnerability and structural inequity. Biologically, the high prevalence of oncogenic viruses (HHV-8, EBV, HPV), the potential pathogenicity of HIV-1 subtype C, host genetic diversity, and the immune impact of endemic co-infections such as tuberculosis and malaria create an environment for accelerated carcinogenesis.

The literature review provides the essential epidemiological and pathophysiological framework for interpreting these empirical findings. It establishes that the elevated risk of specific cancers in PLWH is primarily driven by HIV-induced immunosuppression, which impairs immune surveillance and control of oncogenic viruses, leading to a high burden of associated malignancies such as cervical cancer and Kaposi sarcoma (11, 12, 31). This mechanistic understanding contextualises the findings from the empirical study, which confirmed a high prevalence of these virus-associated cancers (14). Furthermore, the review explains the persistent cancer risk observed in our cohort, where all HIV-positive patients were on ART, by highlighting the role of chronic immune activation and inflammation, which sustain a pro-oncogenic environment even after virological suppression (12). HPV and HIV-1 are both established carcinogens, and residual immune abnormalities and chronic inflammation persist even after apparent immune reconstitution with ART, maintaining conditions favourable for tumour development.

The review also clarifies the complex epidemiology of non-AIDS-defining cancers. The lack of a significant association with prostate cancer in our study aligns with broader evidence suggesting that observed incidence rates are heavily influenced by screening disparities and healthcare access rather than indicating a true biological null association (32). These insights underscore that HIV does not uniformly increase cancer risk but selectively amplifies malignancies with strong infectious etiologies while modifying the biological behaviour of others.

Structural determinants amplify this biological risk. Cervical cancer screening uptake among women living with HIV in SSA remains as low as 30% (23), and our findings of advanced disease stages and diagnostic bias in prostate cancer reflect systemic failures. Limited diagnostic infrastructure, severe shortages of oncology specialists, fragmented referral pathways, and financial and geographic barriers result in late presentation and incurable disease. The KZN phenotype is therefore not an inevitable consequence of biology but a preventable outcome of a syndemic where virological, immunological, and social determinants intersect.

In conclusion, this thesis demonstrates that the HIV–cancer association in KwaZulu-Natal constitutes a distinct syndemic driven by persistent immune dysfunction and systemic inequities. The success of ART has shifted the crisis from AIDS to oncology, creating a dual burden that demands a redefinition of programmatic success beyond viral suppression to include cancer-free survival. Addressing this challenge requires integrated service delivery that embeds cancer screening within HIV care, a dedicated African research agenda to investigate unique biological drivers, and equity-focused health policies to address structural barriers. The HIV–cancer syndemic in KwaZulu-Natal is an intensifying reality that necessitates a unified, resilient health system capable of confronting this dual burden and ensuring that the benefits of ART are not overshadowed by preventable, late-stage cancer.

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APPENDIX: ETHICS

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

20 June 2025

Dr Joyce Adidja (225067175)
School of Laboratory Medicine & Medical Science
Medical School

Dear Dr Adidja,

Protocol reference number: BREC/00008300/2025
Project title: Prevalence of HIV associated cancer amongst individuals of African descent
Degree: Masters

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application.

The conditions have been met and the study is given full ethics approval and may begin as from 20 June 2025. Please ensure that any outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is valid for one year from 20 June 2025. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on RIG on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2024), South African National Good Clinical Practice Guidelines (2020) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at https://research.ukzn.ac.za/research-office/ethics-overview/biomedical-research-ethics/.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on 08 July 2025.

Yours sincerely,

[redacted]

Prof S Singh
Chair: Biomedical Research Ethics Committee

Biomedical Research Ethics Committee
Chair: Professor S Singh
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