Breast cancer in women living with HIV in sub-Saharan Africa: Presentation, diagnosis, and survival.

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Thesis submitted in accordance with the requirements for the award of the degree of Doctor of Philosophy (PhD)

University of London

FEBRUARY 2024

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Declaration

I, Steady J.D. Chasimpha, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed

Date: February 2024

Acknowledgments

I am sincerely grateful to my main PhD supervisor Professor Isabel Dos-Santos-Silva and my second PhD supervisor Dr Valerie Mccormark, without whom this PhD would not have been possible. I first met Val in 2015 during my first visit to International Agency for Research on Cancer (IARC) in France. I was working at Malawi Cancer Registry (MCR) at the time. My boss had strongly instructed me to introduce myself to Val during the visit. Little did I know that the interaction would later lead to a strong working collaboration between IARC and MCR. In 2018, I approached Val for PhD opportunities. She was very keen and introduced me to Isabel, who also did not hesitate to take me on as my main supervisor at LSHTM. Together, they have continually supported me throughout my PhD journey. I would not have completed this work without their expertise, guidance, and above all, their patience. They have remained dedicated to the work, from PhD funding applications to reviewing all manuscripts and drafts of this thesis.

I would also like to thank all co-authors of all research papers that have shaped this thesis for their suggestions and contributions. In particular, I would like to thank Professor Judith Glynn who also very instrumental to the PhD including providing some of the data used in the PhD. I wish to extend the same gratitude to the entire ABC-DO study team in all participating countries, and colleagues at the UNAIDS, who provided the data for my PhD. Without them this PhD would not have been possible.

I am grateful to the Commonwealth Scholarships Commission in the UK for providing me with a scholarship that enabled me to complete my PhD training at LSHTM.

I am also thankful to my fellow PhD students, colleagues, and friends, especially Deus Thindwa, Orlagh Carroll, Rutendo Muzambi, Liang-Yu Lin, Mengyu Liu, Huan Zhang, Olive Mukendi, Ping-Jen Chen, and many others, for all the laughs, conversations and support.

Lastly, I would like to thank my parents and siblings for their prayers, support, and encouragement. My special thanks to my loving wife Diana and daughter Tiyamike Chasimpha who have always been there for me and endured difficult times with me during the PhD. They were patient and understanding and supported/encouraged me with a smile and kind words during moments of doubt and panic.

Abstract

Background: Breast cancer is the commonly diagnosed cancer in women worldwide. Although not a HIV-associated cancer, it is the commonest cancer in women living with HIV. Sadly, these women experience higher mortality rates than their HIV-uninfected counterparts. However, the underlying mechanisms for observed breast cancer survival disparities by HIV status are poorly understood because existing research has been limited by either small sample sizes or lack of granularity needed to properly investigate potential survival determinants.

Aim: This thesis investigated the impact of HIV on the whole breast cancer care continuum from symptom(s) recognition, confirmatory diagnosis, to post-diagnosis journey (survival) in HIV-infected women in sub-Saharan Africa, relative to HIV-uninfected breast cancer women.

Methods and results: Because HIV status was self-reported in most ABC-DO study sites (main PhD data source), I first assessed the validity and accuracy of self-reported HIV-positive status among 17,445 adults who tested and had been informed of their HIV test results in the Karonga Health Demographic Surveillance System (chapter 4). I compared self-reported HIV status and HIV test results, and estimated sensitivity, specificity, positive and negative predictive values for self-reported HIV status. I found very high level of agreement between HIV-self-reports and HIV-test results. Among true HIV-positive individuals, those who were older and had been interviewed in clinic settings were more likely to accurately report their HIV-positive status.

I then examined differences in patient's journey to breast cancer diagnosis, and breast tumour characteristics at diagnosis between HIV-infected and HIV-uninfected women using data from ABC-DO study (chapter 5). There was no evidence for an association between HIV status and the time interval from first breast cancer symptoms to definitive diagnosis, and tumour characteristics (grade, stage, and receptor subtypes) at breast cancer diagnosis. I further investigated differences in overall survival after a breast cancer diagnosis by HIV status, and their determinants among ABC-DO women (chapter 6) and showed that HIV-infected women had increased risk of all-cause mortality compared with HIV-uninfected women (3-year overall survival = 46% vs 55%; adjusted hazard ratio (aHR) 1.42, 95% CI: 1.15 – 1.74). The HIV survival differential was stronger among women with non-metastatic breast cancer (52% vs 65%, aHR 1.65: 1.30 – 2.10). Finally, using UNAIDS mortality data to generate HIV-specific life tables (for relative/net survival estimation) (chapter 7), I showed that HIV-infected women still experienced poorer net survival than HIV-uninfected women. However, there were only a slight difference between mortality rate ratios from overall and net survival estimates (aHR 1.41: 1.13 – 1.75 vs. 1.38: 1.09 – 1.76 respectively), suggesting that the observed survival disparities were not primarily driven by higher background mortality associated with HIV/AIDS in HIV-infected patients.

Conclusion: In summary, I found no association between HIV status and time to breast cancer diagnosis and tumour characteristics at cancer diagnosis. HIV-infected women were at an increased risk of all-cause mortality compared with HIV-uninfected women, even after considering differences in HIV-associated background mortality between the two groups. To prevent more deaths in this unique population, more studies with more granular data on both HIV and breast cancer are needed to evaluate the influence of treatment, treatment-related toxicities, and HIV-related factors.

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Abbreviations and acronyms

ABC-DO	African BC – Disparities in Outcomes
ADC	AIDS defining cancers
AIDS	Acquired immunodeficiency syndrome
ALPHA	Analysis of Longitudinal, Population-based HIV/AIDS data in Africa
ART	Antiretroviral therapy
BCS	Breast conservation surgery
BMI	Body mass index
CI	Confidence interval
CIN	Chemotherapy-induced neutropenia
GLOBOCAN	Global Cancer Observatory
HDSS	Health and demographic surveillance system
HIC	High income country
HIV	Human immunodeficiency virus
HR	Hazard ratio
IARC	International Agency for Research on Cancer
INDEPTH Health	International Network of Demographic Evaluation of Populations and their
KM	Kaplan Meier
KPS	Karonga Prevention Study
LSHTM	London School of Hygiene & Tropical Medicine
LTFU	Loss-to-follow-up
MESH	Medical subject headings
NACT	Neo-adjuvant chemotherapy
NADC	Non-AIDS-defining cancers
NCD	Non-communicable diseases
NPV	Negative predictive value
OR	Odds ratio
PECOS	Population, exposure, comparator, outcomes, and study characteristics
PLWH	People living with HIV
PPV	Positive predictive value
PR	Prevalence ratio
RDI	Relative dose intensity
SABCHO	South African Breast cancer HIV Outcomes study
SEP	Socio-economic position
SSA	Sub-Saharan Africa
TM	Total mastectomy

UNAIDS	United Nations Joint Programme on HIV/AIDS
WHO	World Health Organization
WLWH	Women living with HIV

Chapter 1 Background

1.1 Introduction

In this chapter, I describe the background and rationale for this thesis. I present an overview of the epidemiology of breast cancer, and HIV in sub-Saharan Africa (SSA). I then describe the burden of breast cancer in HIV-infected women, highlight the research gaps and conclude by outlining the thesis aims and specific objectives. At the end of the chapter, I also present the structure of this thesis.

1.2 Burden of breast cancer in sub-Saharan Africa (SSA)

Female breast cancer, a potentially curable malignancy if detected and treated early, is now the most commonly diagnosed cancer globally[1]. According to GLOBOCAN 2020, there were an estimated 2.3 million new cases of breast cancer and 685,000 deaths worldwide (~129,415 new cases and 64,234 deaths in SSA). Historically, incidence rates of breast cancer have remained lower in SSA compared to high-income countries (HICs). The age standardized (to the World standard population) breast cancer incidence rates range from 32.7 to 33.0, 41.5 and 50.9 per 100,000 in Middle, Eastern, Western and Southern Africa compared to 89.4 and 90.7 per 100,000 in Northern America and Western Europe respectively (Figure 1.1).

However, incidence rates of breast cancer in SSA are rising rapidly[1,2]. Firstly, the on-going demographic and economic transition resulting in increase in life expectancy with women in SSA now living longer to ages of increased risk of breast cancer. Secondly, the increasing prevalence of breast cancer risk factors through adoption of ‘western’ life style and changes in reproductive patterns (e.g. delayed childbearing, having fewer children and less breastfeeding) due to economic improvements, means that women in SSA countries now have risk profiles that are becoming similar to those of women in HICs[2,3].

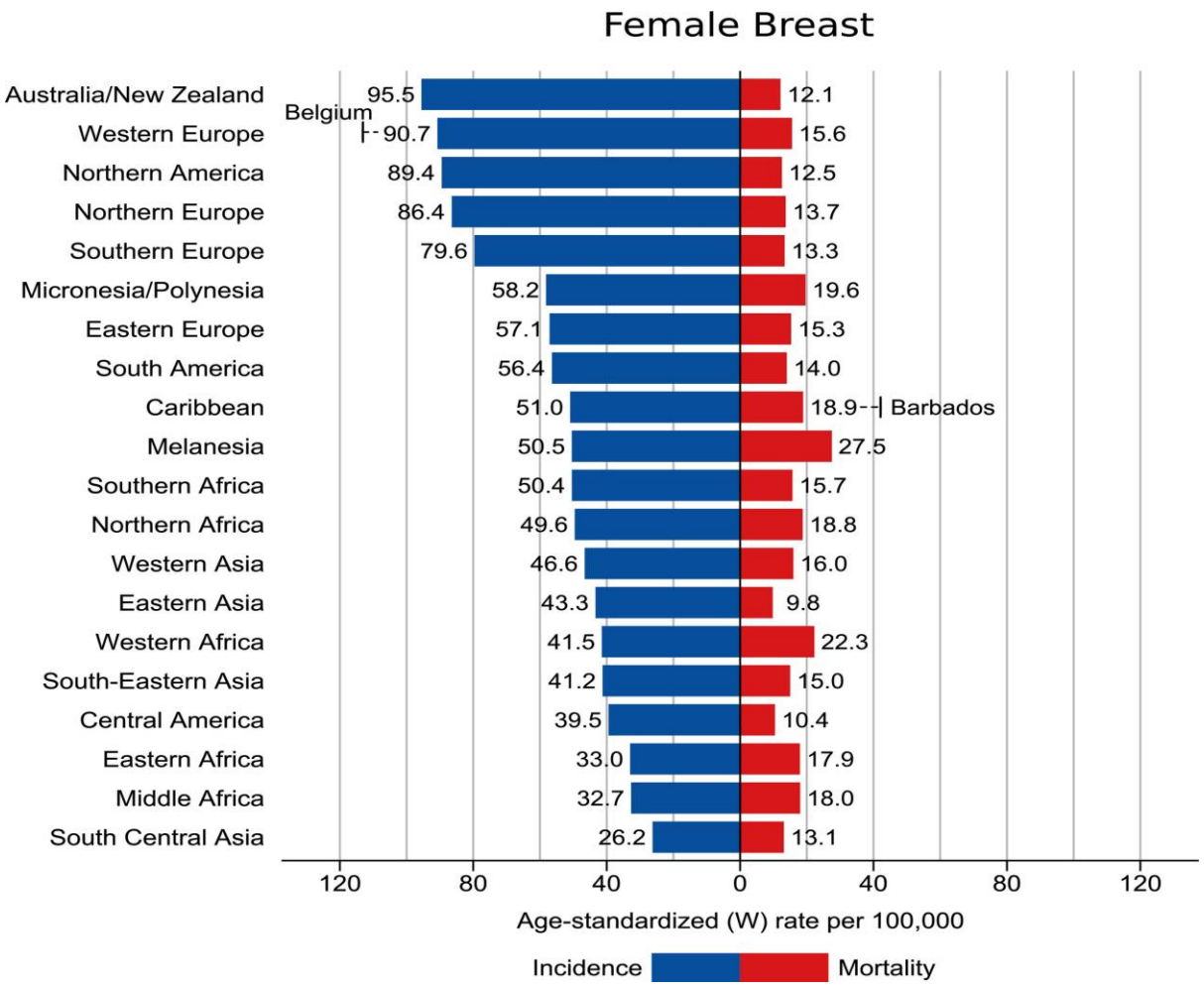
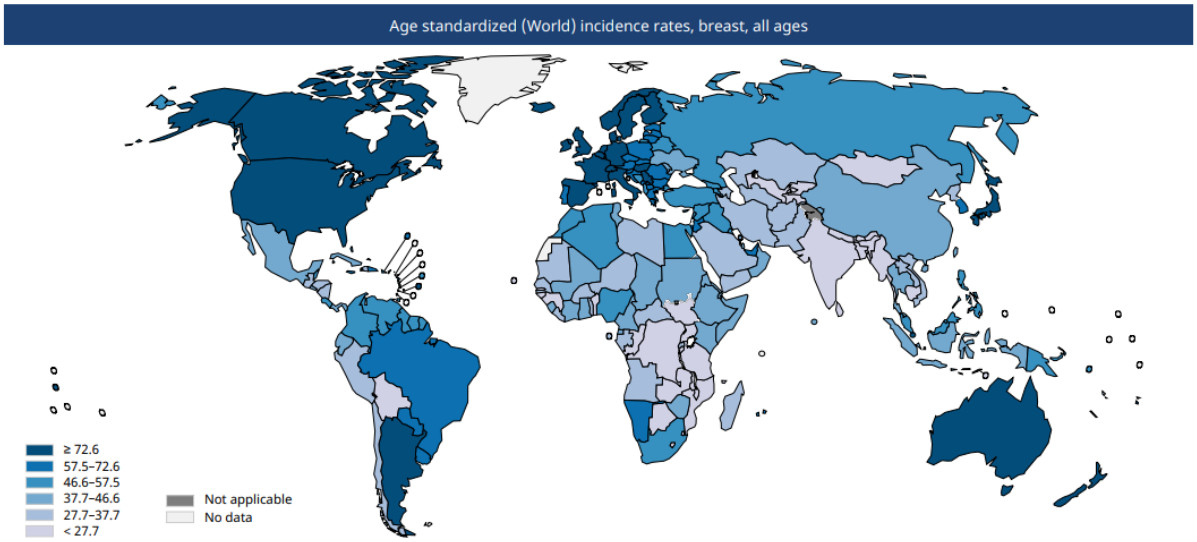


Figure 1.1 GLOBOCAN Estimates of breast cancer incidence and mortality rates in 2020 by World regions per 100,000 women[1] (W: World standard population)

Despite low incidence, breast cancer mortality rates in SSA are highest in the world (Figure 1.2 a & b). The estimated 5-year age-standardised relative survival in most countries in SSA (<50% vs. >85% in most HICs) are comparable to estimates observed in HICs such as USA and Norway over three decades ago. The lower survival rates in SSA are attributable to late-stage disease at presentation due to low breast cancer awareness (of both patients and health care workers), lack of access to effective treatments and huge burden of comorbidities such as HIV[4,5].

(a)



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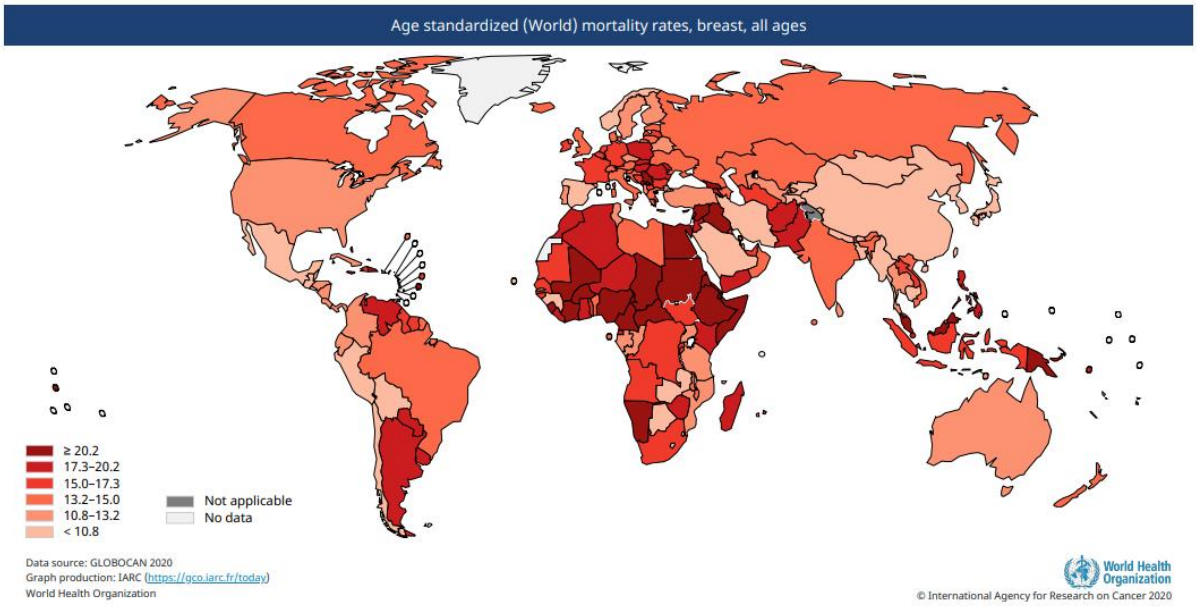


Figure 1.2 Age-standard incidence (a) and mortality (b) rates of breast cancer Worldwide, per 100,000 women in 2020 (GLOBOCAN 2020 Estimates[6])

1.3 Burden of HIV in sub-Saharan Africa

HIV remains a major global public health issue despite the tremendous progress in prevention and treatment with anti-retroviral therapy (ART). The AIDS response, particularly the expanded access to ART, has led to declining numbers of new HIV infections and a 38% reduction in AIDS-related deaths between 2010 and 2022[7]. Despite these gains, the global HIV burden remains substantial. In 2022, there were 39.0 million (95% confidence interval (CI): 33.1 - 45.7) people living with HIV globally (Figure 1.3), 1.3 million (1.0 - 1.7) people became newly infected with HIV, and 630,000 (480,000-880,000) people died from AIDS-related illnesses[7]. SSA, particularly Eastern and Southern Africa, bears the largest HIV burden worldwide with nearly two thirds (66%) of all people living with HIV. Of the 39.0 million people living with HIV, 20.8 million were in Eastern and Southern Africa[7,8].

The HIV epidemic in SSA disproportionately affects women and girls more than men, accounting for 63% of all new infections in 2022[7]. Adolescent girls and young women in SSA are twice as likely to be living with HIV than men of the same age[7]. These inequalities are driven by gender power dynamics, unequal cultural, socio and economic status[9,10]. For example, low socio-economic status may compel girls and young women to engage in transactional sex with older men who may already have been exposed to the virus.

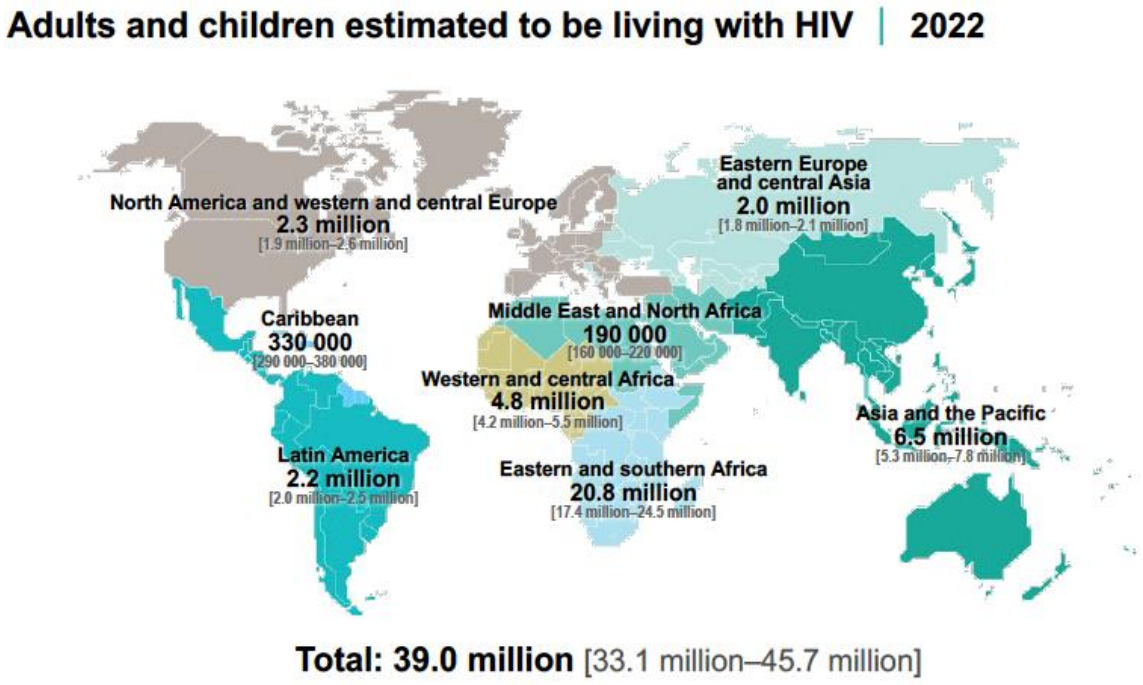


Figure 1.3 Number of people living with HIV Worldwide 2022 (Source: UNAIDS 2022 Epidemiological estimates[7])

1.3.1 Scaling up of anti-retroviral therapy for HIV

The expansion of HIV treatment guidelines in 2015 by the WHO, to include all persons with HIV regardless of CD4 count and clinical stage of AIDS, has led to associated gains in life expectancy and substantial decline in HIV/AIDS-related mortality. The latest UNAIDS estimates indicate that in 2022, 29.2 million people living with HIV were accessing anti-retroviral therapy (ART) compared to 7.7 million in 2010. More women than men were accessing ART (82% of female adults aged 15 years and older had access to ART compared to 72% of men of the same age). During the era of ART, AIDS-related mortality has reduced by 51% since 2010 (Figure 1.4). In 2022, there were 630,000 AIDS-related deaths worldwide compared to 1.3 million in 2010. These declines are slightly greater in women and girls (55%) than among men and boys (47%).

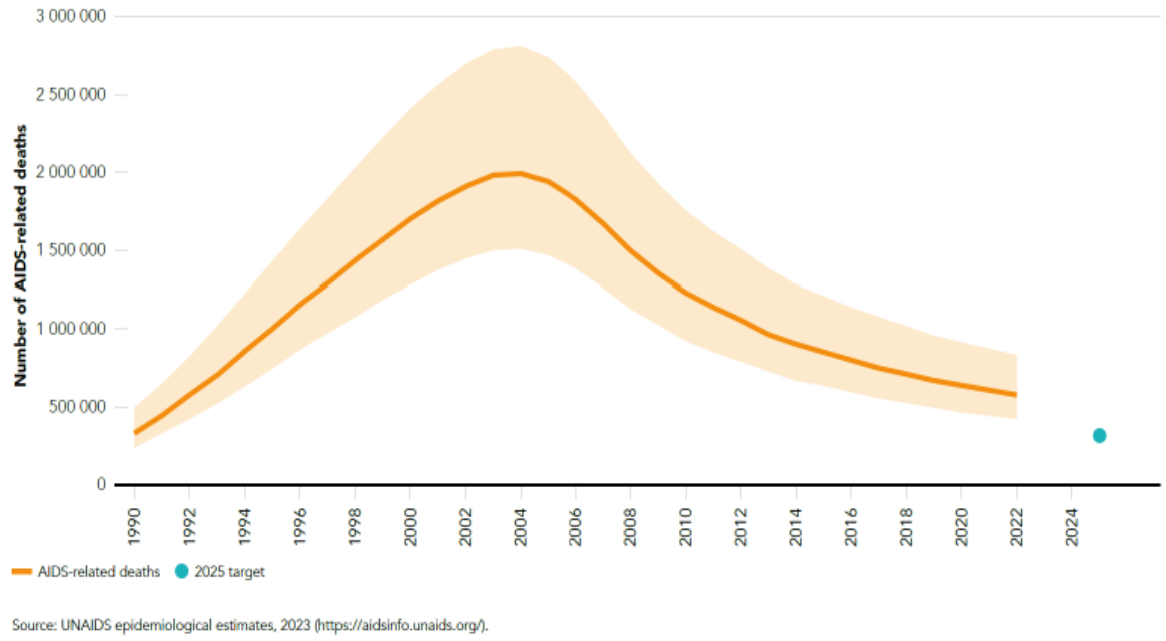


Figure 1.4 Global trends in AIDS-related deaths, 1990-2022 (UNAIDS 2022 HIV Estimates[7])

As the HIV epidemic matures and more people get access to ART, the number of people living with HIV will increase coupled with increased longevity to ages when risk of non-communicable diseases such as cancer is high.

1.4 HIV and breast cancer

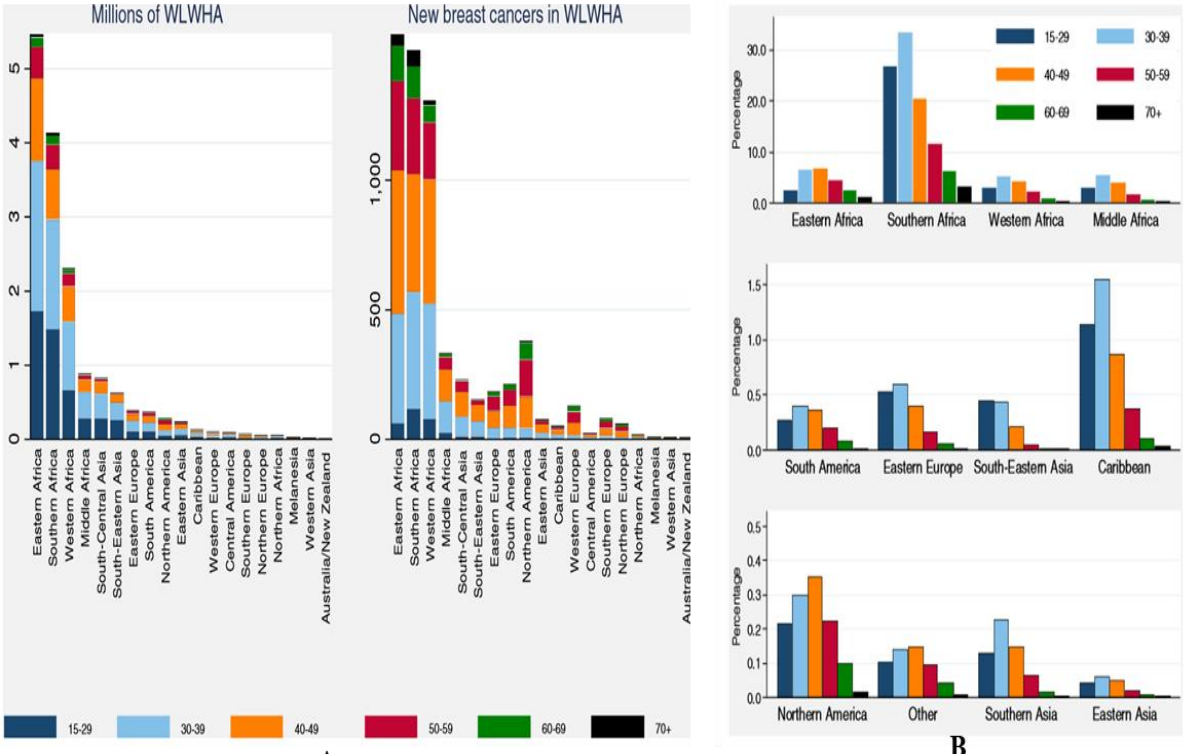
Unlike cervical cancer, Non-Hodgkin lymphoma and Kaposi sarcoma which are known AIDS-defining cancers (ADCs)[11-13], there is no established association between HIV and breast cancer risk. While the introduction of ART resulted in dramatic decrease in incidence rates of ADCs worldwide, there has been a three-fold increase in the absolute numbers of some non-AIDS defining cancers (NADCs) such as lung and oesophageal cancer among HIV-positive people[12,14,15]. Similar trends, albeit modest, have been reported in SSA countries such as Botswana, South Africa and Malawi[16-18]. As the number of older women living with HIV continues to increase due to ART the absolute numbers of NADCs are expected to increase. This rise will be particularly marked for breast cancer as this malignancy is one of the most commonly diagnosed in women (second to cervical cancer in most SSA countries), and its incidence is anticipated to double in SSA by 2050[4,19].

1.4.1 Incidence of breast cancer in women with HIV

Several studies form North America[12,20], Europe[21] and SSA[22-25], have documented breast cancer in women living with HIV. Research, pre- and early-ART era, suggested that incidence rates of breast cancer in women living with HIV were lower than in women in the general population. A meta-analysis of 18 studies, all of which were from high-income countries, showed significantly lower standardized incidence ratio (SIR) for breast cancer in women living with HIV (compared to the general population) of 0.7 (95% CI: 0.56-0.97)[26]. However, more recent studies have clearly shown increase in absolute numbers of breast cancer cases in women living with HIV mainly because of improvements in life expectancy due to ART. Following introduction of ART in the US, absolute numbers of breast cancer in the US AIDS population increased 10-fold[12]. In a report that included 151 HIV-positive (vs. 614 HIV-negative) breast cancer patients in Soweto, South Africa, HIV prevalence among breast cancer patients did not differ to that of the source population (RR 1.20, P=0.13)[22].

In 2018, the WHO/International Agency for Research on Cancer (IARC) published the first ever estimates of global burden of breast cancer in women living with HIV. The report showed that globally, women living with HIV constitute less than 1% of all patients with breast cancer, but in high HIV-prevalence settings, such as Southern Africa, women living with HIV represent 25% of the clinical burden especially among women aged less than 50 years[27]. Among 16.0 million women living with HIV (aged 15 years and over) worldwide, 6,325 were diagnosed with breast cancer in 2012, 74% of whom were in sub-Saharan Africa. Figure 1.5 below shows estimated numbers of women living with HIV and the corresponding absolute and age-specific proportions of newly diagnosed breast cancer cases in 2012, by

UN sub-region. While Eastern Africa had more women living with HIV (5.5 million), a large proportion of breast cancers occurred in Southern Africa because of its higher incidence rates of breast cancer. The majority (70%) of women living with HIV were younger (<50 years) at breast cancer diagnosis, reflecting the younger age structure of women living with HIV compared to the general population.



A

Total and age-specific number of women age15+ years living with HIV/AIDS and estimated number of breast cancers in WLWH in 2012, by UN sub-region

B

Age-specific percentage of newly diagnosed breast cancer patients who are HIV-positive, by UN sub-region.

Source: **McCormack et al.** Int. J. Cancer:143,2732–2740 (2018)©2018 UICC

Figure 1.5 Estimated n*u*mber of women living with HIV and absolute incidence of breast cancer in HIV-infected women by UN sub-regions

1.4.2 Disparities in HIV/breast cancer outcomes in women with HIV

Overall, HIV-infected women diagnosed with breast cancer have been shown to experience increased risk of mortality compared to their HIV-uninfected counterparts, even after taking into account age and stage at cancer diagnosis. This may be expected as HIV-infected women have, in general, higher all-mortality rates compared to the general population, due to HIV/AIDS-related mortality. Published estimates of the excess all-cause mortality in HIV-infected women range from 40%-60% increase in South Africa and Mozambique to 80%-

100% in Botswana and Uganda[24,28-31]. In North America, HIV-infected women were associated with an adjusted 50% and 80% increased risk of all-cause and breast cancer-specific mortality, respectively[32,33]. However, most of these estimates, especially from sub-Saharan Africa, are based on studies with either small numbers of women living with HIV, sub-optimal follow-up time or high-losses-to-follow-up (LTFU).

1.5 Problem statement and research gaps

The direct and indirect impact of HIV infection on multiple aspects of the breast cancer journey is under-researched, including on clinical presentation, tumour characteristics, treatment and related toxicities, and survival. There is a consensus that HIV-infected breast cancer patients experience higher mortality rates compared to breast cancer women without HIV, yet the pathways behind these disparities are not fully understood.

Figure 1.6 below outlines potential pathways through which co-presence of HIV and breast cancer may lead to poorer overall survival in HIV-infected women diagnosed with breast cancer compared to breast cancer women without HIV. Firstly, survival deficits in HIV-infected women may occur if they have poorer prognostic factors for breast cancer. HIV-infected women are diagnosed with breast cancer at younger ages compared their HIV-uninfected counterparts. This is not surprising and should not be interpreted as evidence of more aggressive tumours in HIV-infected women. It simply reflects the younger age structure of HIV-positive women compared to women in the general population. However, younger age at diagnosis has been shown to be a poor prognostic factor for breast cancer regardless of HIV status[34,35]. Another important prognostic factor is stage at breast cancer diagnosis. However, there is little/unclear evidence that stage at cancer diagnosis differs by HIV status. Studies in the US indicate that HIV-infected women are more likely to be diagnosed with advanced-stage tumours while most studies in SSA have shown either no such differences or only a slightly higher prevalence of advanced-stage tumours among HIV-infected patients. Similarly, there is little/unclear evidence that HIV-infected women have breast cancer with more aggressive tumour pathology, whether BMI differs by HIV status, and whether HIV treatment may have an effect on breast tissue[26].

Secondly, the higher mortality experience among HIV-infected women may reflect potential differences in treatment and clinical management between HIV-infected and HIV-uninfected women. HIV-infected women may receive modified treatment regimens, reduced doses and/or delayed treatment because of other conditions associated with HIV, resulting in receiving sub-optimal breast cancer treatment compared to their HIV-negative counterparts.

Additionally, HIV-infected women may experience HIV and cancer drug-to-drug interactions leading to intensified treatment-related toxicities, and hence low treatment compliance.

Finally, the reported higher mortality in HIV-infected women diagnosed with breast cancer may simply be because they have higher background mortality than women in the general population. Immunosuppression and higher prevalence of comorbidities may lead to higher background mortality in women living with HIV either through AIDS-related mortality or higher mortality from other causes. However, fewer studies, all from the US, have examined breast cancer-specific mortality in HIV-infected women, which is not affected by differences in background mortality[32,36,37]. Such studies have shown that HIV-infected women had 1.5- and 1.9-fold increased breast cancer-specific mortality compared to their HIV-uninfected counterparts. To date there are no similar studies yet in SSA.

In summary, as the HIV epidemic in SSA matures and access to ART increases, more HIV-infected women will become affected by both HIV and breast cancer and hence there is a need to clarify the reasons for the poorer overall survival after a breast cancer diagnosis experienced by HIV-infected women relative to their HIV-uninfected counterparts. Although several studies have been conducted in the US, few have been conducted in SSA, home to 75% of the HIV-infected breast cancer patient population. More research is needed to address the research gaps outlined above to improve outcomes in this unique patient population.

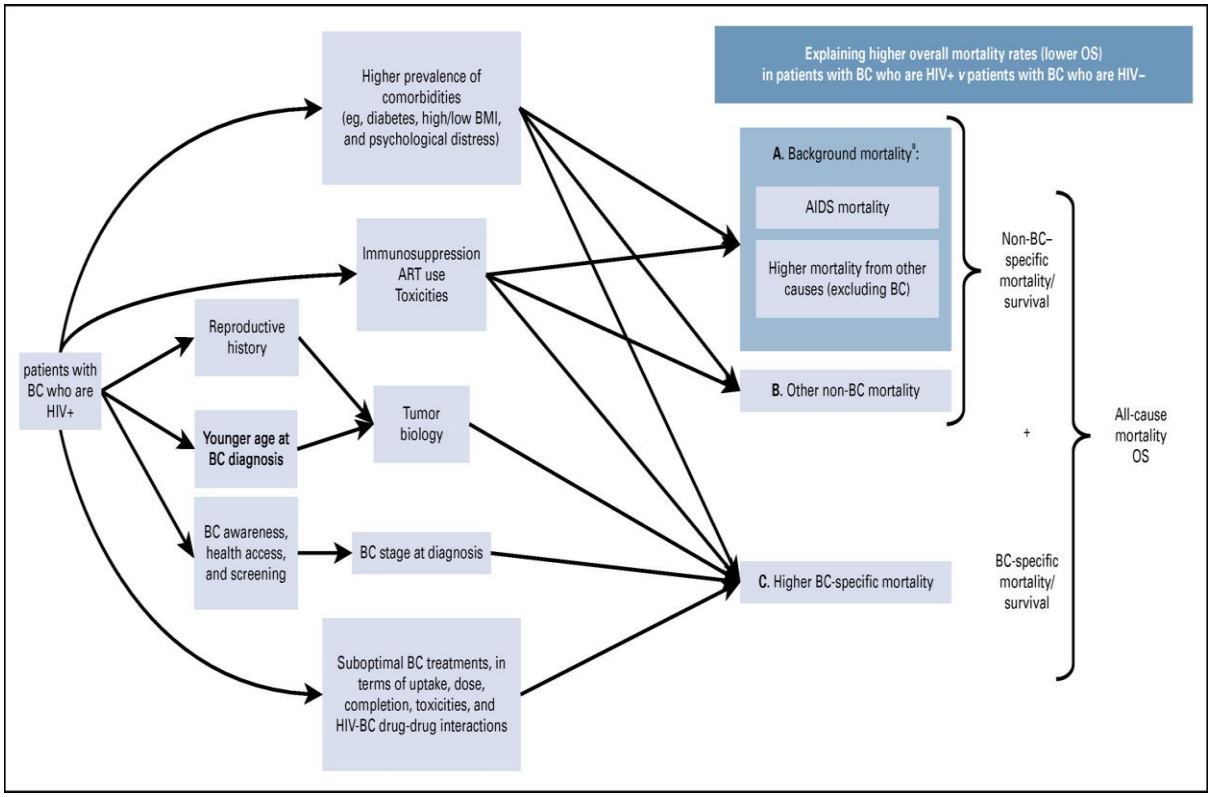


Figure 1.6 Potential pathways leading to higher overall mortality rates (lower OS) in patients with HIV and breast cancer. a) Taken into account through relative (net) survival. ART, antiretroviral therapy; BC, breast cancer; OS, overall survival

(Source: Steady Chasimpha; Isabel dos Santos Silva; Yehoda M. Martei; Surbhi Grover; Herbert Cubasch; Valerie McCormack; JCO Global Oncology 2023 9e2200330. DOI: 10.1200/GO.22.00330[38])

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1.6 Aim and specific objectives of my PhD thesis

1.6.1 Aim

The aim of this thesis is to investigate the impact of HIV on the whole breast cancer care continuum from symptom(s) recognition, confirmatory diagnosis, to post-diagnosis journey (survival) in women living with HIV in SSA, relative to HIV-negative breast cancer women.

1.6.2 Specific objectives

(1) To assess the validity of self-reported HIV-status information, and identify predictors of accurate self-reporting of an HIV-positive status in SSA;

(2) To examine differences in patient's journey to breast cancer diagnosis, and breast tumour characteristics at diagnosis by HIV status;

(3) To examine differences in overall survival after a breast cancer diagnosis by HIV status overall and by country, and their determinants; and

(4) To examine relative survival after a diagnosis of breast cancer in HIV-infected women relative to their HIV-uninfected counterparts

1.7 Thesis outline

This thesis uses the *"research paper style"* approach which combines a set of related manuscripts that are either published or prepared for publication. Three of the eight chapters of this thesis are already published articles, and another chapter is manuscript already prepared for publication at the time this thesis was written. Each of these articles is accompanied by a cover letter and a short description clearly outlining the objectives of the paper and how it links to previous chapters and the entire thesis, and an additional short discussion of the results where necessary.

In chapter 2, I present the results of a systematic literature review conducted to summarise the available evidence on the relationship between HIV and breast cancer. It highlights research gaps and limitations of previous studies.

In chapter 3, I provide a detailed description of the data sources/studies used in this thesis i.e., the African Breast Cancer – Disparities in Outcomes (ABC-DO) study, the Karonga Health and Demographic Surveillance records and the UNAIDS HIV estimates. These include the study settings, summary of study protocols, and study strengths and limitations.

Chapter 4 is a published research paper on the accuracy and validity of self-reported HIV status. The main data source for this thesis is the ABC-DO study, a generic hospital-based prospective cohort of women diagnosed with breast cancer rather than an HIV-focused one. As such, some of the HIV-related information in the ABC-DO study was self-reported. Thus, the goal of the work carried in this chapter was to assess accuracy and validity of self-reported HIV status information by using data from individuals who had tested for, and were informed of their HIV status in other SSA settings similar to ABC-DO settings. The manuscript is published in AIDS Journal[39].

In chapter 5, I examine whether time from when a woman notices her first breast cancer symptoms to the time of a confirmatory breast cancer diagnosis differs by HIV status. This is important as the length of the pre-diagnostic journey might be related to tumour stage at diagnosis - a strong prognostic factor for breast cancer. The results from this work were presented in a poster at the 2019 AORTIC Conference in Maputo, Mozambique.

In chapter 6, a research paper published in the Lancet HIV, I examine the differences in, and determinants of, overall survival after a breast cancer diagnosis between HIV-infected and HIV-uninfected women. I present results of estimated three-year overall survival after a breast cancer diagnosis in women with and without HIV in the prospective multi-country ABC-DO study, for all participating sites combined, and for each country separately. The paper also identifies groups of HIV-infected women with breast cancer at a particularly high risk of all-cause mortality following the cancer diagnosis.

Chapter 7 provides results of estimated relative (net) survival for women with breast cancer by HIV status. I carried out this analysis to investigate whether the increased risk of all-cause mortality observed after a breast cancer diagnosis among HIV-infected women compared with their HIV-uninfected counterparts is simply due to the higher background mortality associated with HIV/AIDS among women with HIV. This chapter is also a manuscript, prepared for publication in the International Journal of Cancer.

Chapter 8 provides a summary of the main findings from the thesis as well as conclusions and implications drawn from this work. The chapter outlines strengths and limitations, and recommendations for future research building on work presented in this thesis. In this chapter, I also highlight some of the epidemiological considerations that should be addressed to clarify the underlying reasons for survival differentials between breast cancer women with and without HIV – these considerations have been published as a commentary[38] in the Journal of Global Oncology.

1.8 Role of the candidate

The research questions addressed in this thesis were already conceived by my supervisors through their work within the ABC-DO study. I led preparation of application for, and secured research funding through the PhD scholarship from the Commonwealth Scholarship Commission in the UK. With guidance from supervisors, I conducted the systematic literature review, prepared statistical analysis plans, and performed all analyses. I prepared first drafts of all chapters and manuscripts, edited the drafts according to co-authors' comments and was responsible for the final draft and submission for publication, and further revisions upon reviewer's comments, of all research papers presented in this thesis.

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Chapter 2 Literature review

2.1 Introduction

Despite having a larger proportion of HIV-infected breast cancer patients, there are few published studies on the impact of HIV on breast cancer in sub-Saharan Africa (SSA). Most of the available literature on this topic have come from studies conducted in North America. As part of this thesis, I conducted a systematic literature review of studies investigating the relationship between breast cancer and HIV in SSA. The main objective of the review was to summarise published research findings related to breast cancer and HIV in SSA.

Particularly, the systematic review was undertaken to understand current state of knowledge and research about the impact of HIV on breast cancer in SSA with a focus on pre-diagnostic journey, tumour features, treatment, and survival, to:

- Identify research graphs and limitations of existing literature, and
- Inform the development of this thesis in light the of available published findings.

The review will highlight the strengths and limitations of previous studies and will identify the areas for which research findings have so far been inconsistent. At the end of the chapter, I will discuss the type of research which is required in the region to clarify these issues.

2.2 Scholarly databases, key words, and search strategy

Several health and medical databases were systematically searched for relevant peer-reviewed research articles. These included EMBASE, MEDLINE, Global Health, Africa Wide Information, SCOPUS, and Web of Science. However, grey literature, unpublished articles and hand searching of relevant journals were not used.

Key concepts/search terms used were “breast cancer”, “HIV/AIDS” and “Sub-Saharan Africa”. A search strategy using these keywords and Medical Subject Headings (MESH) terms, complemented by Boolean operators, was developed, and adapted to each individual database, including all possible synonyms and without any language restrictions. The literature searches were initially performed in January 2019, at the start of my PhD, and re-run in September 2023, at the writing stage, to identify new articles published between January 2019 and September 2023. Table 2.1 below is an example of search strategy used in Medline database.

Table 2.1 Literature search strategy used in Medline database

DATABASE	SEARCH STRATEGY
Medline	1. (breast or mammary) N4 (cancer* or neoplasm* or malignan* or tumor? or carcinoma) 2. breast neoplasms 3. 1 OR 2 4. hiv or aids or acquired human immunodeficiency syndrome or human immunodeficiency virus 5. hiv infection 6. S4 OR S5 7. Africa 8. Africa or sub-Saharan Africa or Angola or Benin or Botswana or Burkina Faso or Burundi or Cameroun or cape Verde or Chad or central African republic of Comoros or Congo or Cote d'Ivoire or democratic republic of Congo or equatorial guinea or Eritrea or Ethiopia or Gabon or Gambia or Ghana or Guinea or Guinea-Bissau or Kenya or Lesotho or Liberia or Madagascar or Malawi or Mali or Mozambique or Namibia or Niger or Nigeria or Rwanda or Soa Tome or Senegal or Seychelles or Sierra Leone or Somalia or south Africa or Swaziland or Togo or Uganda or Tanzania or Zambia or Zimbabwe 9. 7 OR 8 10. 3 AND 6 AND 9

2.2.1 Inclusion and exclusion criteria

The focus of the review was on studies related to breast cancer and HIV conducted in SSA countries. Retrieved articles from search strategy were screened for potential eligibility based on title and abstract content. Full texts of identified papers were sought to review further if they met inclusion criteria (see Table 2.2 below). I screened and reviewed all articles with a random sample cross-checked by a second reviewer (supervisor).

Table 2.2 Inclusion and exclusion criteria

	Included studies	Excluded studies
Population and conditions of interest	• Women aged 15 and above • Enrolled patients with both breast cancer and HIV	• Non-human studies • Enrolled patients with breast cancer only or HIV only • Male breast cancer only
Publication type	• Original research articles • Published in all languages	• Conference abstracts/meeting proceedings • Commentaries • Review papers
Study designs	• All study designs	• None
Study geographical location/setting	• Sub-Sahara Africa only • All settings whether hospital or population-based	• North Africa • Outside Africa

2.2.2 Data extraction

Data were extracted from each included paper according three thematic areas namely tumour characteristics cancer at diagnosis, treatment characteristics and overall survival after a breast cancer diagnosis. A data extraction form was designed based on the Population, Exposure, Comparator, Outcomes and Study characteristics (PECOS) framework, to capture the following data items.

Population: Age at breast cancer diagnosis (mean/median), ethnicity, socio-economic status.

Exposure: HIV-positive status, how it was measured (self-reported/tested), number of HIV-infected breast cancer patients, other breast cancer risk factors.

Comparator: HIV-uninfected breast cancer patients.

Outcomes:

1. Tumour and treatment characteristics including tumour grade and stage at breast cancer diagnosis, tumour hormone receptor status, treatment type and related toxicities
2. Breast cancer outcomes – survival probabilities, mortality hazard ratios for HIV status

Study characteristics: Authors, title, publication year, country, study design and population, sample size, setting, duration of follow-up and eligibility criteria

2.2.3 Data analysis

Due to smaller numbers of, and heterogeneity of research designs and study variables/outcomes in included studies, a meta-analysis was not performed. Results of this review are therefore, presented as content analysis of each included paper according to thematic areas outlined in section 2.2.2.

2.3 Results

2.3.1 Search strategy results

The initial literature search, conducted at the beginning of the PhD and covering the period up to January 2019, identified 9 articles/papers. The updated search, conducted at the start of the writing-up of this thesis, covered the period between January 2019 and September 2023, identified an additional 10 papers. These included papers from the ABC-DO study which were included in the present review except for specific work covered in this thesis. The degree of consistency of the PhD findings with those from other published ABC-DO analyses, and other studies will be discussed in later chapters.

Results of both searches are presented together excluding the research paper that arose from my PhD work[1], which is described in detail in chapter 6.

In total, the review included 18 articles. Figure 2.1 shows the results of the searches conducted including the number of articles included in the review and those excluded at each stage of the review process. After de-duplication of results from all searched databases, 473 potential articles were identified, of which 431 (91%) were subsequently excluded through title and abstract screening. Of the remaining 42 studies, full texts were retrieved for 35 studies as seven excluded because they were conference abstracts. Full text screening resulted in further exclusion of 17 (46%) studies because they either did not include patients with both HIV and breast cancer, included overlapping populations or males or only presented number of HIV-infected breast cancer participants without exploring association between HIV status and outcomes of interest (for this review). Finally, 18 articles were included in the review; four articles on clinical features and tumour characteristics[2-5], six articles on treatment characteristics[6-11]; and eight articles on survival after a breast cancer diagnosis[12-19]. Some of the articles included in the review relate to the same study (although for different research objectives); six articles used data from the South African

Breast Cancer and HIV Outcomes (SABCHO) study and four articles used data from Chris Baragwanath Academic Hospital (Table 2.3).

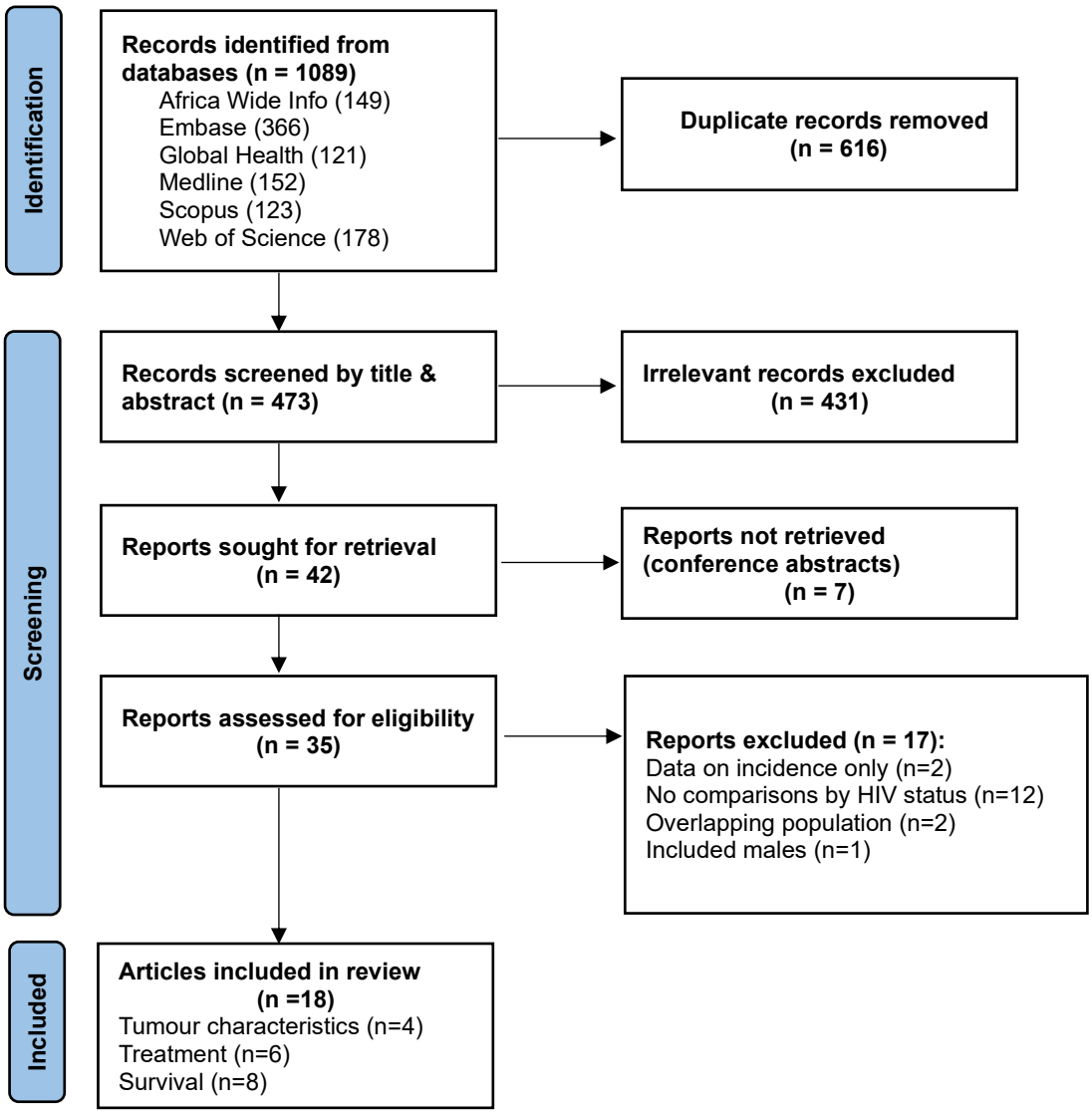

Figure 2.1 PRISMA Flow diagram describing systematic literature search and article selection

2.3.2 Study characteristics

The characteristics of the 18 eligible studies, and their results are summarized in Table 2.3 and Table 2.4 respectively. These studies were conducted in South Africa (n=13); Uganda (n=1); Botswana (n=2); Guinea (n=1), Malawi (n=1); and the ABC-DO study which was done in five countries – South Africa, Namibia, Uganda, Nigeria, and Zambia. In total, four studies investigated the association between HIV status and tumour characteristics at breast cancer diagnosis[2-5], six studies were on treatment characteristics[6-11], and eight studies estimated

overall survival after a breast cancer diagnosis in HIV-infected versus HIV-uninfected women[12-19]. The number of HIV-infected women with breast cancer included in these studies varied widely, ranging from as low as 14 (vs. 246 HIV-uninfected women) to 499 (vs. 1868).

Table 2.3 Characteristics of studies included in the review

Author (Year) /Setting	Study design (study years)	Eligibility criteria	HIV exposure assessment	No. of HIV+ / HIV- BC women
	Tumour characteristics			
Cubasch et al (2013)[2] South Africa	Retrospective cohort (2003-2010)- based on ambient data at the Chris Baragwanath Academic Hospital (CHBAH)	Incident breast cancer women diagnosed at CHBAH	HIV testing done	151/614
Traore et al (2015)[4] Guinea	Retrospective cross-sectional (2007-2012)	Women with breast cancer seen at Donka National Hospital	HIV testing done	14/278
Zyl van et al (2018)[5] South Africa	Retrospective cross-sectional (2013-2017)- based on ambient data at Dr George Mukhari Academic Hospital (DGMAH)	Incident breast cancer women diagnosed at DGMAH	HIV status documented in patient records	49/80
Phakathi et al (2019)[3] South Africa	Retrospective cross-sectional (2015-2017)- based on ambient data at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and CHBAH	Women aged 18 or older, with incident breast cancer diagnosed at CMJAH and CHBAH	HIV testing done	226/790
	Treatment characteristics			
Phakathi et al 2016[11] South Africa	Prospective cohort (2009-2014)	Women with breast cancer undergoing surgery at the Steve Biko Academic Hospital	HIV testing done	31/129
Ngidi et al (2017)[9] South Africa	Retrospective case series (2012-2015)	Women with breast cancer treated at the Inkosi Albert Luthuli Central Hospital	HIV status as documented in patient records	21/44
Cubasch et al (2017)[7] South Africa	Retrospective case series (2009-2011)- based on hospital records at CHBAH	Adult patients newly diagnosed with invasive carcinoma of the breast excluding those with metastatic disease	HIV testing done	59/373
Martei et al (2020)[8] Botswana	Prospective cohort (2017-2019) – study of patients newly diagnosed breast cancer at princess Marian Hospital, Botswana	Women age 18 or older, newly diagnosed with stage I-III breast cancer and initiating NACT*	Self-reported HIV status	26/110
Nietz et al (2020)[10] South Africa	Prospective cohort (2015-2018) – based on data from SABCHO[20]** study	Women aged 18 or older, newly diagnosed with stage I-III breast cancer and had received at least 2 cycles of NACT	HIV testing done	173/715
Ayeni et al (2023)[6]	Prospective cohort (2019-2021) – based on data from SABCHO** study	Women aged 18 or older, newly diagnosed with stage I-III breast cancer and initiated tamoxifen	HIV testing done	78/369
	Survival after breast cancer diagnosis			
Coghill et al (2013)[13] Uganda	Retrospective cohort (population-based 2003-2010) – based on Kampala Cancer Registry Database and medical records at Uganda Cancer Institute and Mulago Hospital	Adults aged at least 18 years at diagnosis of common cancers including breast cancer	HIV ascertained based on documented positive HIV antibody test, medical history of HIV infection and an HIV clinic referral letter	24 / 196
Cubasch et al (2018)[14] South Africa	Retrospective cohort (2009-2014)- based on routine hospital data at CHBAH	Incident breast cancer women diagnosed at CHBAH	HIV testing done	88 /411

Author (Year) /Setting	Study design (study years)	Eligibility criteria	HIV exposure assessment	No. of HIV+ / HIV- BC women
McCormack et al (2020)[15] Namibia, South Africa, Nigeria, Uganda, Zambia	Prospective (hospital-based) cohort (2014-2019)	Women aged 18 or older, newly diagnosed with primary breast cancer	Self-reported (and tested HIV in South Africa only) status	315/1841
Youngblood et al (2020)[19] Malawi	Prospective cohort (2016-2018) – based on study of newly diagnosed breast cancer patients at Kamuzu Central Hospital, Lilongwe	Women aged 18 or older with newly diagnosed, pathologically confirmed breast cancer	HIV testing done	19/100
Phakathi et al (2021)[17] South Africa	Prospective cohort (2015-2017) – based on data from SABCHO** study	Women aged 18 or older, newly diagnosed with primary breast cancer	HIV testing done	221/764
Pumpalova et al (2021)[18] South Africa	Prospective cohort (2015-2019) – based on data from SABCHO** study	Women aged 18 or older, newly diagnosed with stage IV primary breast cancer	HIV testing done	147/403
Ayeni et al (2022)[12] South Africa	Prospective cohort (2015-2019) – based on data from SABCHO** study	Women aged 18 or older, newly diagnosed with stage I-III primary breast cancer	HIV testing done	499/1868
Phakathi et al (2023)[16] South Africa	Prospective cohort (2015-2019) – based on data from SABCHO** study	Women aged 18 or older, newly diagnosed with breast cancer and were eligible for PAM50 intrinsic subtypes analysis	HIV testing done	176/200

HIV+: HIV-infected; HIV-: HIV-uninfected; BC: breast cancer; SABCHO: South African Breast Cancer and HIV Outcomes study; NACT: neoadjuvant chemotherapy

Table 2.4 Summary of main results of studies included in the review

Author (Year) /Setting	Main statistical analysis methods used	Main reported crude results	Main reported adjusted results / Variables adjusted for
	Tumour characteristics		
Cubasch et al (2013)[2] South Africa	Generalised linear models to estimate prevalence ratios (PR)	19.7% HIV prevalence HIV+ breast cancer patients younger than HIV-patients with one-third of patients aged <50 were HIV+ No evidence for differences in stage (PR=0.98), tumour grade (0.60) and tumour receptors by HIV status	PR=1.18 (95% CI: 0.68-1.32) for stage III vs. stages I&II in HIV+ vs. HIV- women PR=1.06 (0.92-1.23) for ER+ vs. ER- in HIV+ vs. HIV- women Adjusted for: age at cancer diagnosis and year of cancer diagnosis
Traore et al (2015) [4] Guinea	Median and percentages	5% HIV prevalence Median age at diagnosis was 37 (IQR, 36-40) in HIV+ vs. 49 (20-85) in HIV- women No difference in tumour characteristics by HIV status	Not done
Zyl van et al (2018)[5] South Africa	Mean and percentages	38% HIV prevalence Mean age at diagnosis was 45 (SD, 9 years) in HIV+ vs. 54 (12) in HIV-women	Not done
Phakathi et al (2019)[3] South Africa	Generalised linear models to estimate prevalence ratios	22% HIV prevalence Median age at diagnosis was 45 (IQR, 40-52) years in HIV+ vs. 57 (46-67) in HIV- women HIV+ women more likely to present with late-stage breast cancer (PR, 1.36 (95% CI: 1.07-1.73)) No difference in tumour subtypes by HIV status Duration of HIV seropositivity not associated with tumour characteristics	Stage at diagnosis did not differ by HIV status in adjusted models (PR, 1.12 (0.90-1.39) Adjusted for: age (linear), ethnicity (black vs. non-black women)
	Treatment characteristics		
Phakathi et al 2016[11] South Africa	Logistic regression	31% HIV prevalence HIV+ women mean age 41 (SD, 9) vs. 55 (14) in HIV-women No difference in tumour characteristics between HIV+ and HIV- women NO significant differences in surgery and related complications by HIV status Risk ratio (RR) for occurrence of surgical complications = 0.20 (0.03-1.45)	Adjusted RR for occurrence of surgical complications = 0.24 (0.03-1.82) Adjusted for: Age and stage at cancer diagnosis
Ngidi et al (2017)[9] South Africa	Kaplan Meier curves for incidence of neutropenia Cox proportional hazard models	32% HIV prevalence HIV+ women younger (mean age 40 (10) than HIV- women, 52 (13)) HIV+ women were at increased risk of neutropenia (HR, 2.1 (1.39-3.18))	Adjusted HR 1.76 (1.06-2.92) Adjusted for: age at cancer diagnosis

Author (Year) /Setting	Main statistical analysis methods used	Main reported crude results	Main reported adjusted results / Variables adjusted for
Cubasch et al (2017)[7] South Africa	Logistic regression models	16% HIV prevalence 354 (80%) underwent total mastectomy vs. 91% who had breast conserving surgery HIV status was not associated with type of surgery in univariate analysis	HIV+ patients were more likely to receive total mastectomy than breast conserving surgery, compared with HIV- patients (Adjusted OR, 3.19 (1.30-7.90)) Adjusted for: age, stage at diagnosis, and tumour molecular subtypes
Martei et al (2020)[8] Botswana	Linear and logistics regression models Cox proportional hazard models	24% HIV prevalence HIV+ women were younger, more likely to be overweight or obese and hormone receptor-positive disease Pathologic complete response (pCR) was significantly lower in HIV+ patients HIV+ patients had significantly lower mean relative dose intensity (RDI) of NACT vs. HIV-patients (RDI=0.70 (0.61-0.79) vs. 0.81 (0.76-0.85), Chi-squared p=0.028) HIV+ women with worse 2-year overall survival (unadjusted HR, 2.68 (1.17-6.13) Toxicity rates were similar between HIV+ and HIV- women despite HIV+ patients receiving lower dose intensity chemotherapy	In adjusted analyses, there was no difference in pCR rates between HIV+ and HIV- women (adjusted OR=0.28 Adjusted for: BMI, RDI and hormone receptor status Survival analyses and analyses on toxicity rates not adjusted for
Nietz et al (2020)[10] South Africa	Logistic regression models	24% HIV prevalence HIV+ patients less likely to achieve pCR than HIV- women (15 (9%) vs. 89 (14%, p=0.01) Age-adjusted OR for pCR in HIV+ vs. HIV- women = 0.47 (0.26-0.85)	Fully adjusted OR = 0.52 (0.28-0.98, p=0.04) Adjusted for: age, stage at diagnosis, tumour receptor status, BMI
Ayeni et al (2023)[6]	Logistic regression models	21% HIV prevalence Median (IQR) concentration of tamoxifen was lower in HIV+ vs. HIV- women (25.9ng/mL, IQR: 15.7-74.5 vs. 56.0: 29.1-101.0, Chi-squared p<0.001) HIV+ women were twice as likely as HIV- women to be non-adherent to tamoxifen ()R=2.16 (1.26-3.70), p=0.005)	Non-adherence in HIV+ patients was 2.4 times that in HIV-women (Adjusted OR= 2.40 (1.11-5.20), p=0.03) Adjusted for: education, time on tamoxifen, combined tamoxifen side effects, and CYP2D6 predicted phenotype
	Survival		
Coghill et al (2013)[13] Uganda	Kaplan Meier curves Cox proportional hazard models	11% HIV prevalence 6/23 HIV+ vs. 23/196 HIV-patients died within 1 year of follow-up HIV+ women had increased risk of all-cause mortality, though not statistically significant (HR=1.98, 0.74-5.28) adjusted for age and year of cancer diagnosis Most patients were uniformly diagnosed with advanced-stage disease regardless of HIV status	Fully adjusted HR= 2.04 (0.76-5.47) Adjusted for age and stage at diagnosis, and year of cancer diagnosis
Cubasch et al (2018)[14]	Kaplan Meier curves	15% HIV prevalence	Adjusted HR for HIV+ vs. HIV- women = 1.39 (0.83-2.33)

Author (Year) /Setting	Main statistical analysis methods used	Main reported crude results	Main reported adjusted results / Variables adjusted for
South Africa	Cox proportional hazard models	48% loss to follow-up at the end of 4 years HIV+ women had slightly higher risk of death than HIV- women although not statistically different	Adjusted for: age, tumour grade an stage at diagnosis, and tumour receptor status
McCormack et al (2020)[15] Namibia, South Africa, Nigeria, Uganda, Zambia	Kaplan Meier curves Cox proportional hazard models and flexible parametric models	15% HIV prevalence Very low (<5%) loss to follow-up 139/315 HIV+ had died vs. 740/1841 HIV- women HIV+ women had increased risk of death than HIV- women	Adjusted HR = 1.48 (1.22-1.81) Adjusted for: age and stage at cancer diagnosis (Note: Women with unknown HIV status classified as HIV-uninfected)
Youngblood et al (2020)[19] Malawi	Kaplan Meier curves Cox proportional hazard models	19% HIV prevalence Lower 1 year overall survival in HIV+ women (71% (43-84)) vs. HIV- women (73% (58-84)) HIV+ patients were associated with increased risk of all-cause mortality (HR= 1.46, 0.61-3.48)	Adjusted HR= 5.15 (1.58-16.8) Adjusted for: age and stage at diagnosis, and tumour molecular subtype
Phakathi et al (2021)[17] South Africa	Kaplan Meier curves Cox proportional hazard models	22% HIV prevalence Compared to HIV-women: Unadjusted HR for HIV+ women= 1.50 (1.22-1.85) for Unadjusted HR for HIV+ women on ART = 1.28 (1.00-1.63 Unadjusted HR for HIV+ women not on ART = 2.10 (1.52-2.91)	Adjusted HR for HIV+ vs. HIV- women = 1.77 (1.37-2.28, p<0.001) Adjusted for: age at diagnosis (continuous), BMI (continuous), stage at diagnosis, receptor subtype, employment status, and education
Pumpalova et al (2021)[18] South Africa	Kaplan Meier curves Cox proportional hazard models	27% HIV prevalence No difference by HIV status for receipt fo chemotherapy, palliative surgery or hormonal therapy (HR+ tumours only) Among these women with stage IV diseases, 1-year overall survival was lower for HIV+ women (48.8% (40.5-56.5)) vs. HIV-women (60.7% (55.7-65.3)), albeit not statistically significant (p=0.09)	HIV status was not associated with overall survival (Adjusted HR= 1.13 (0.89-1.44), p=0.32) Adjusted for: age and stage at diagnosis, treatment hospital, performance status, hormone receptor status, HER2 receptor status, Ki67, metastatic site, receipt of systemic treatment and palliative surgery
Ayeni et al (2022)[12] South Africa	Kaplan Meier curves Cox proportional hazard models	21% HIV prevalence 190/499 HIV+ women died vs. 538 (1868) HIV- women HIV+ women had poorer overall survival at 2 years than did HIV-women (72.4% vs. 80.1%, p=0.004) overall; whether they had stage I-II disease (84.3% vs90.8%, p=0.002) or ER+/PR+ tumours (76.1% vs. 83.1%, p<-.001) or ER-/PR- tumours (60.6% vs. 69.1%, p=0.04) All-cause mortality was higher in HIV+ women vs. HIV- women (HR= 1.45 (1.23-1.72))	Adjusted HR=1.49 (1.22-1.83), p<0.001 Adjusted for: age at diagnosis, ethnicity, education level, BMI, ECOG PS, stage at diagnosis, tumour subtype, Ki67, and treatment received,

Author (Year) /Setting	Main statistical analysis methods used	Main reported crude results	Main reported adjusted results / Variables adjusted for
Phakathi et al (2023)[16]	Kaplan Meier curves	47% HIV prevalence	Adjusted mortality HR = 2.14 (1.58-2.90)
South Africa	Cox proportional hazard models	Regardless of intrinsic subtype, HIV+ women had poorer 5-year survival than did HIV-women (34.1% vs. 59.6%, p<0.001)	Adjusted disease recurrence HR= 2.26 (1.62-3.16)
		5-years disease-free survival was much worse in HIV+ vs. HIV-women (23.9% vs. 59.6%, p<0.001)	Adjusted for: age and stage at diagnosis
		Unadjusted mortality HR= 2.08 (1.55-2.80)	
		Unadjusted disease recurrence HR = 2.30 (1.65-3.19)	

CI: confidence interval; ER+: eostrogen receptor positive; ER-: Eostrogen receptor negative; HIV+: HIV-infected; HIV-: HIV-uninfected; HR: hazard ration; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HER2: human epidermal growth factor receptor 2; BMI: body masss index; ART: antiretroviral therapy; pCR: pathologic complete response; RDI: relative dose intensity.

2.3.3 Patient and tumour characteristics at cancer diagnosis

HIV-infected women were diagnosed with breast cancer at younger ages than did HIV-uninfected women. The reported median age at breast cancer diagnosis in HIV-infected women ranged from median 37 years (IQR: 36-40) to 45 years (40-52) compared with 49 (20-85) to 57 (46-67) in HIV-uninfected women. In Soweto, South Africa, one-third of all women aged <50 years were HIV-infected[2]. The distribution of tumour characteristics (tumour grade, stage, and hormone receptor status) at cancer diagnosis did not differ between HIV-infected and HIV-uninfected women. HIV-infected women were as likely to be diagnosed with advanced-stage disease as did HIV-uninfected women. Similarly, there was no evidence for a difference in the distribution of breast tumour molecular subtypes by HIV status. Most breast tumours were hormone-receptor positive (i.e., oestrogen receptor positive and/or progesterone receptor positive) regardless of HIV status. In a South African study where high-quality information on hormone receptor status was available, more than 75% of breast tumours were oestrogen receptor positive (74% in HIV-infected vs. 75.9% in HIV-uninfected women)[3].

2.3.4 Treatment characteristics by HIV status

Six studies identified in the review characterised breast cancer treatment in HIV-infected women relative to HIV-uninfected women in SSA. The first study looked at incidence of chemotherapy-induced neutropenia (CIN). HIV-infected women had 76% increased incidence of CIN (age adjusted hazard ratio HR, 1.76; 95% CI:1.06-2.92). Although ART did not protect against incidence of CIN, women with HIV receiving ART had lower grades of CIN and less severe complications compared with those not on ART[9].

In another study by Phakathi et. al.[11], which included 31 HIV-infected women (vs. 129 HIV-uninfected women), there were no statistically significant difference in the number of patients who completed treatment (chemotherapy or radiation) between HIV-infected and HIV-uninfected patients. HIV-infected women did not experience more surgical complications than their HIV-uninfected counterparts. In fact, HIV-uninfected women experienced more complications than did HIV-infected women. However, this may have been because most HIV-uninfected patients were, on average, older[11]. In terms of treatment decisions, HIV status was associated with type of surgery procedure (total mastectomy vs. breast conserving surgery). Relative to HIV-uninfected women, HIV-infected women were more likely to undergo total mastectomy than breast conserving surgery even after adjusting for age, tumour stage at diagnosis and molecular subtypes (adjusted odds ratio, OR; 3.19: 95% CI, 1.30-7.90)[7].

In a study that evaluated response to systemic therapy, HIV-infected patients were less likely to achieve pathologic complete response to neoadjuvant chemotherapy (NACT) than did their HIV-uninfected counterparts (adjusted OR; 0.52: 95% CI, 0.28-0.98) even after adjusting for age, BMI, stage, estrogen receptor (ER)/progesterone receptor (PR) status and human epidermal growth factor receptor (HER2) status. Similar findings were reported by Martei et. al.[8], in their study in which only 5% (1/20) HIV-infected patients achieved complete pathological response (vs. 21% (14/52); OR = 0.20, in HIV-uninfected patients). This finding, however, was not statistically significant in multivariable analyses probably due to the small sample size. The mean relative dose intensity (RDI) was significantly lower in HIV-infected women compared with HIV-uninfected women. Approximately half (40/84) of HIV-uninfected patients received NACT treatment with RDI ≥ 0.85 compared with less than one-third (7/26) in HIV-infected patients[8]. HIV-infected women were as likely as HIV-uninfected women to experience grade ≥ 3 toxicity despite a lower RDI in former group[8].

Ayeni et. al.[6], investigated the association between HIV status and adherence to adjuvant tamoxifen among women with localized hormone receptor-positive breast cancer in South Africa. They showed that women who were non-adherent to tamoxifen were more likely to be younger (<40 years old) and HIV-infected (55/208 (22.6%) vs. 23/161 (14.3%), p=0.003) than women who were adherent. HIV-infected women were twice as likely as HIV-uninfected women to be non-adherent to tamoxifen (adjusted OR; 2.40: 95% CI, 1.11-5.20)[6].

2.3.5 Survival following breast cancer diagnosis

In total, eight studies estimated survival following a breast cancer diagnosis in SSA (Table 2.4). In all studies, HIV-infected were consistently associated with increased risk of all-cause mortality compared with HIV-uninfected women. These studies differed widely in terms of study population, number of HIV-infected participants, duration of follow-up and study populations. Sample sizes were generally smaller with shorter duration of follow-up in earlier studies leading to statistically insignificant differences in risk of mortality between HIV-infected and HIV-uninfected women. For example, the reported all-cause mortality adjusted HRs for HIV-infected women were 2.04 (95% CI, 0.76 – 5.47) and 1.39 (0.83 – 2.33) in studies from Uganda (2013, HIV-infected women = 24/196)[13] and South Africa (2018, n=88/411)[14] respectively. In more recent studies, sample size tended to be larger except for one study from Malawi by Youngblood et. al., which included only 19 HIV-infected women (vs. 100 HIV-uninfected). Despite the small sample size, HIV-infected women in this study still had increased risk of all-cause mortality than their HIV-uninfected counterparts (adjusted HR 5.15 (1.58 – 16.8)), albeit with very wide 95% confidence intervals. In other studies, number of HIV-infected women ranged from 147 (vs. 403 HIV-uninfected women) to 499 (vs.

1868). One of these studies was from our ABC-DO cohort and reported an increased risk of all-cause mortality in HIV-infected women compared with HIV-infected (n= 315/1841, adjusted HR 1.48 (1.22-1.81)[15]. Noteworthy, in this study, women with unknown HIV status were classified as HIV-uninfected.

Two of the studies investigated survival disparities between HIV-infected and HIV-uninfected women in defined patient groups based on stage at diagnosis. The first study by Pumpalova et. al., which was restricted to women with stage IV breast cancer, reported no differences in risk of all-cause mortality between HIV-infected and HIV-uninfected women (adjusted HR 1.13, 0.89 – 1.44)[18]. In contrast, Ayeni et. al.[12], reported a significant difference in all-cause mortality between HIV-infected vs. HIV-uninfected among women with stage I-III breast cancer at diagnosis (adjusted HR for HIV-infected women 1.49, 1.22 – 1.83)[12]

2.4 Discussion

In this chapter, I have provided an overview of current knowledge on the relationship between HIV and breast cancer with a focus on publications relevant to SSA. The literature review has included evidence or lack thereof, for association between HIV status and patient/tumour characteristics at breast cancer diagnosis, treatment and related complications, and survival.

Overall, HIV-infected women are diagnosed with breast cancer at younger ages compared with HIV-uninfected women reflecting essentially a cohort effect rather than an age effect. HIV prevalence is higher among more recent younger cohorts of women compared to older cohorts. Generally, similar trends have also been reported in studies from North America. However, one study showed that age at diagnosis in the US AIDS and general population did not differ for breast cancer[21]. Thus, as the HIV epidemic matures in SSA, it is to be expected that age at breast cancer in HIV-infected women will reach that of HIV-uninfected women.

There was no evidence of differences in stage at cancer diagnosis by HIV status in SSA. This may be because a large proportion of women in SSA presenting with advanced-stage tumours, regardless of HIV status. In North America, where most women are predominantly diagnosed at early stage, studies showed that HIV-infected women were more likely to present with advanced-stage disease than HIV-uninfected women, with a study reporting that HIV-infected women were nearly twice more likely to be diagnosed with advanced-stage breast cancer than did HIV-uninfected women[22]. There was also no evidence for differences overall regarding distribution of molecular subtypes of breast cancer between HIV-infected

and HIV-uninfected women in SSA, although this was largely based on data from South Africa as, unfortunately, tumour receptor status is not routinely assessed in most SSA settings. Nevertheless, in South Africa HIV-infected women were as more likely to have hormone receptor-positive tumours, the best prognosis subtypes, as HIV-uninfected women.

Generally, HIV-infected women were overall, just as likely to receive similar treatment as HIV-uninfected women. This is consistent with findings from studies in the US where HIV-infected women received stage-appropriate cancer treatment in the year after breast cancer diagnosis just like their HIV-uninfected counterparts[23]. Suneja et al. reported no differences in receipt of standard cancer treatment between HIV-infected and HIV-uninfected women in the USA[24]. However, results from our ABC-DO study showed that HIV-infected women were less likely to receive curative breast cancer treatment than HIV-uninfected women[25]. Noteworthy, available data on treatment of HIV-infected breast cancer women in SSA are either based on small numbers or very crude binary measures of treatment (received/not received) with very few studies on treatment quality or completion. The sparse data on treatment tolerability suggest that women with HIV may experience worse treatment-related side-effects/complications. However, the evidence in SSA was inconclusive. Only one study evaluated treatment adequacy in which HIV-infected women were associated with lower relative dose intensity. There was also only one study on treatment compliance/adherence. HIV-infected women were more likely to be non-adherent to tamoxifen than HIV-uninfected women. Thus, more studies are needed to evaluate whether treatment is modified in HIV-infected (i.e., reduced dosages, delayed treatment), compliance with treatment, and potential ART-cancer drug to drug interactions.

On outcomes, HIV-infected women had consistently worse overall survival after a breast cancer diagnosis compared to HIV-uninfected women. The reported all-cause mortality excess in HIV-infected women ranged from 50% to 80% relative to HIV-uninfected women. These survival disparities were more pronounced in women with non-metastatic breast cancer (i.e., tumour stage I-III) as among women with metastatic diseases (tumour stage IV), all-cause mortality was high regardless of HIV status.

The findings of increased risk of all-cause mortality reported in studies from SSA are consistent with reports from North America. A large USA HIV/AIDS-Cancer Match study showed that HIV-infected women in the USA had 4.6 times and 2.6 times increased risk of all-cause and breast cancer-specific mortality respectively, even after adjusting for age and stage at cancer diagnosis, ethnicity and year of diagnosis[26]. There were no studies evaluating breast cancer-specific survival in SSA nor the reasons for the poor outcomes in HIV-infected women.

The review was based on a comprehensive search of studies using multiple databases with no restriction on date and language. A detailed and peer reviewed strategy was used, increasing the validity of findings. However, there are some limitations. First, grey literature and other sources were not used – other relevant studies may be missed if only available in those sources. Second, due to small number of studies included for each review theme and the heterogeneity of methods used, I was unable to perform meta-analysis. Additionally, studies from outside SSA were excluded hence the review findings are not exhaustive of all published evidence on HIV and breast cancer. However, comparison of findings has been made where possible to studies conducted in other regions.

Despite limitations, the review highlights an important fact that the relationship between HIV and breast cancer in SSA remains under-researched. For example, there was no study investigating the role of HIV status on the pre-diagnostic journey of breast cancer patients. There were also no attempts to investigate reasons for increased risk of mortality after a breast cancer diagnosis among HIV-infected women. For instance, no study has so far investigated the extent to which poorer overall survival experienced by HIV-infected breast cancer women reflects the fact that such women may have higher background mortality due to HIV/AIDS-associated mortality than HIV-uninfected women. Yet, there was no study in SSA that investigate breast cancer-specific survival disparities between the two groups.

2.5 Summary

- In summary, this literature review summarises evidence from published studies in SSA on the relationship between HIV status and breast cancer. A total of 18 studies were included in the review.
- Four studies investigated the association between HIV status and patient/tumour characteristics at diagnosis of breast cancer. HIV-infected women were more likely to be diagnosed with breast cancer at younger ages compared with HIV-uninfected women. However, there was no evidence for differences in tumour grade, tumour receptor subtype or stage at cancer diagnosis, and tumour molecular subtypes between HIV-infected and HIV-uninfected women.
- Breast cancer treatment characteristics were evaluated in six studies. HIV-infected women were as likely to receive standard cancer treatment as HIV-uninfected. However, HIV-infected women were more likely to receive lower doses and to be non-adherent to tamoxifen than their HIV-uninfected counterparts.
- Eight studies estimated survival after breast cancer diagnosis. HIV-infected women were consistently associated with increased risk of all-cause mortality compared with HIV-uninfected women. Most of the studies (in earlier years that aligned with the start of the

PhD) included small numbers of HIV-infected women and had shorter duration of follow-up.

- The review highlighted the need for large studies and research into reasons for survival disparities between HIV-infected and HIV-uninfected women, including investigating the pre-diagnostic journey and potential differences in background mortality.

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Chapter 3 Study settings and data sources

3.1 Introduction

In this chapter, I provide the overview of three data sources used to address the research aims of the thesis. The first data source is the Karonga Health Demographic Surveillance System (HDSS) dataset which I used to investigate the first research aim of assessing the validity of self-reported HIV status. Secondly, I describe the African Breast Cancer-Disparities in Outcomes study. The ABC-DO study is the main data source for this thesis and was used to address research aims two to four. This is followed by a brief description of UNAIDS data on mortality estimates for countries participating in ABC-DO study. I used this additional data source for the fourth research aim which examined net survival disparities between HIV-infected and HIV-uninfected women with breast cancer. For each data source, I outline its aims and objectives, study settings and implementation, and its relevance to achieving the objectives of this thesis. I also discuss the strengths and limitations of each data source.

3.2 Karonga HDSS

A HDSS is a combination of field and computing procedures for collecting epidemiological data (risks, exposures and outcomes) within a defined population on a longitudinal basis[1]. HDSSs cover real-life populations by monitoring births, deaths, cause of death, migration, and other health and socio-economic indicators over time[2].

The Karonga HDSS is situated in Karonga District in rural northern Malawi and is one of thirty-two HDSSs in SSA. The HDSS was established in 2002 as part of the Karonga Prevention Study (KPS). KPS started as a large cohort study of risk factors for leprosy in 1979 but later assumed responsibility for district-wide diagnosis and treatment for infectious diseases including becoming the largest Bacillus Calmette-Guerin (BCG) vaccine trial in Africa against both TB and leprosy. Following studies that established presence of HIV in the area in 1987, HIV became the major research theme at KPS[3].

3.2.1 Rationale for establishing Karonga HDSS

Karonga HDSS was established as a platform for epidemiological studies for HIV and HIV-associated infectious diseases and to monitor the impact of interventions. In addition to generating data on basic demographic indices, cause-specific mortality, population-level routinely collected data on vaccine coverage and socio-economic status, the HDSS also conducts detailed clinical and behavioural studies in individuals to:

(i) Monitor changes in HIV incidence and transmission of drug resistant virus

(ii) Assess changes in sexual behaviours and attitudes

(iii) Measure HIV-attributable mortality and morbidity

(iv) Identify factors affecting anti-retroviral treatments (ART) adherence

(v) Evaluate socio-economic and demographic impact of HIV and estimate future trends in HIV epidemic

(vi) Evaluate the success of HIV interventions

3.2.2 Karonga HDSS setting and study population

The Karonga HDSS covers an area of approximately 135 Km^2 in the southern part of Karonga district. The HDSS surrounds the port village of Chilumba, on Lake Malawi, with boundaries with lake shore to the east and Nyika National Part to the west (Figure 3.1). The study population is predominantly rural although a smaller proportion of the population lives in semi-urban areas (i.e., trading centres). There are now more than 40,000 people registered in over 8,000 households, most of whom are subsistence farmers, fishermen and small-scale traders.

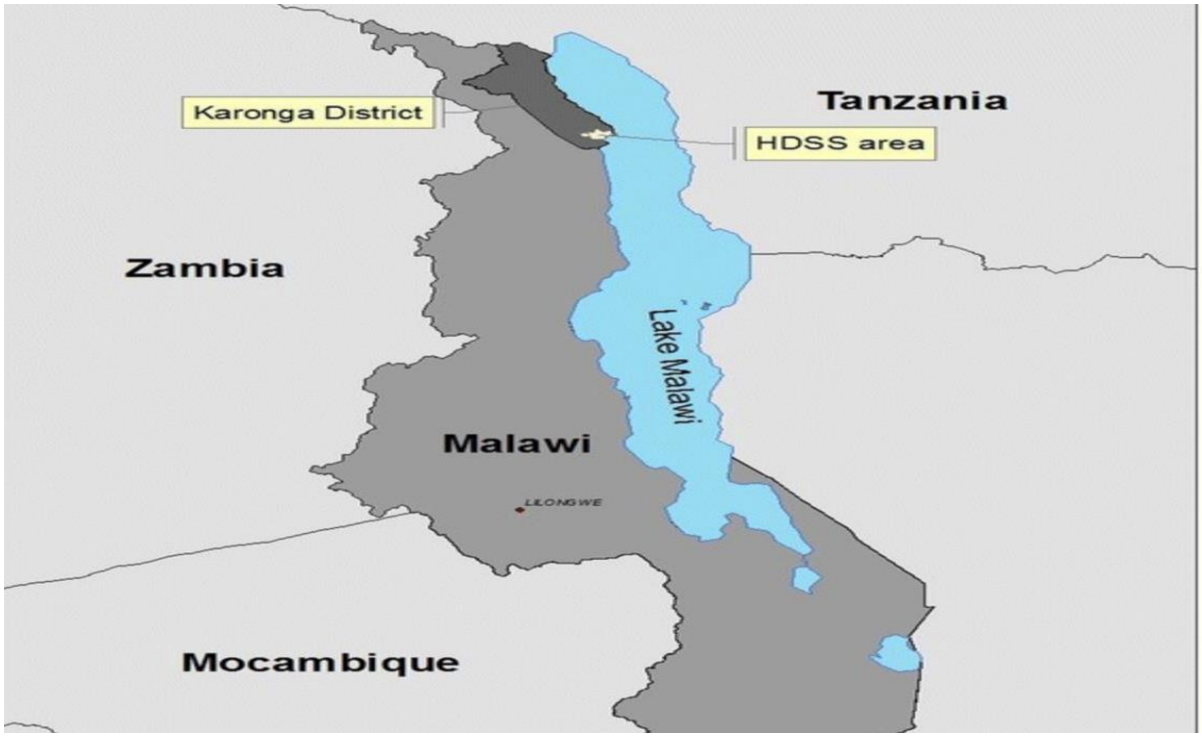

Figure 3.1 Location of Karonga district and the Karonga HDSS in northern Malawi

(Adapted from "Profile: The Karonga Health and Demographic Surveillance System" by Crampin AC et al.[3])

3.2.3 Data collection in the HDSS

Karonga HDSS started with a baseline census of all households in the area in 2002. Clusters consisting of 20-30 households were set up, with a key informant resident identified in each cluster. Key informants were trained to keep a real-time record of vital events (births, deaths and migration) occurring in their cluster. A nominated KPS interviewer then meets with the key informants monthly to update household registers for each cluster. Each individual has a static and unique identity number and continuous registration system number. These are useful especially during annual re-censuses which are conducted to capture migration, check births and deaths, and update socio-economic information. In addition, cause of death information is collected for every reported death via verbal autopsy.

3.2.4 HIV data

As earlier stated, HIV became a major focus of research at KPS since late 1980s. In 2005, Karonga HDSS became a founding member of the ALPHA network for Analysis of Longitudinal, Population-based HIV/AIDS data in Africa, adequately described in these two dedicated publications[4,5]. As part of this network, a sample of HIV sero-survey was conducted between 2005 and 2006[6,7]. By 2011, a total of four surveys had been completed, using different types of rapid tests[7]. Additionally, HIV testing is offered in clinics, research studies and antenatal clinic surveillance programs in the HDSS area and from service providers elsewhere. At each HIV testing opportunity, detailed self-reported data are collected on previous HIV tests including approximate date and results of the most recent HIV test. Consenting participants may choose whether to be informed, or not, of their HIV test results.

3.2.5 Relevance of this data source to the PhD

This thesis is mainly based on data from the ABC-DO study which was a generic breast cancer cohort rather than HIV-focused. As such ABC-DO study protocol did not include HIV testing. Most of available data on HIV status and other HIV-related data in ABC-DO study were self-reported by the women except in South Africa where HIV testing was done. The Karonga HDSS was therefore, used to determine accuracy and identify factors that may influence accurate self-reporting of HIV status in a population that is tested and informed of their HIV test results. The HDSS provided a rich resource as it is large and based on population-based longitudinal HIV data spanning over 10 years. More importantly, the availability of unique identifiers and dates for each HIV test made it possible to link all HIV

test results to corresponding data on subsequent self-reported HIV status and create record pairs between each HIV test result and its self-reported HIV status which enabled assessment of the validity of self-reported HIV status data by comparing self-reported HIV status against the HIV test result.

3.2.6 Limitations of the data source

Karonga HDSS, Malawi is not part of the ABC-DO study. As such, a limitation with using this data source is that the study setting is different from settings included in the ABC-DO study hence findings thereof may not be easily generalizable. The regular sero-surveys and other research studies conducted in the HDSS means that participants are exposed to frequent HIV testing and are aware of their HIV status more than other settings in the region. However, an estimated 86% of people living with HIV are aware of their HIV status[8]. Thus, to some extent, data from the HDSS may be extrapolated to other settings of similar HIV prevalence, such as the ABC-DO settings.

3.3 The African Breast Cancer – Disparities in Outcomes (ABC-DO) study

The ABC-DO study is a within-Africa, multi-country study of factors that affect breast cancer outcomes across different SSA settings. The study aims to comprehensively study the entire breast cancer journey from pre-diagnosis to survivorship, to identify determinants (including sociocultural, biological, treatment-related, and health system factors) of early diagnosis, treatment, and survival from breast cancer. Figure 3.2 below is a conceptual framework for the ABC-DO study.

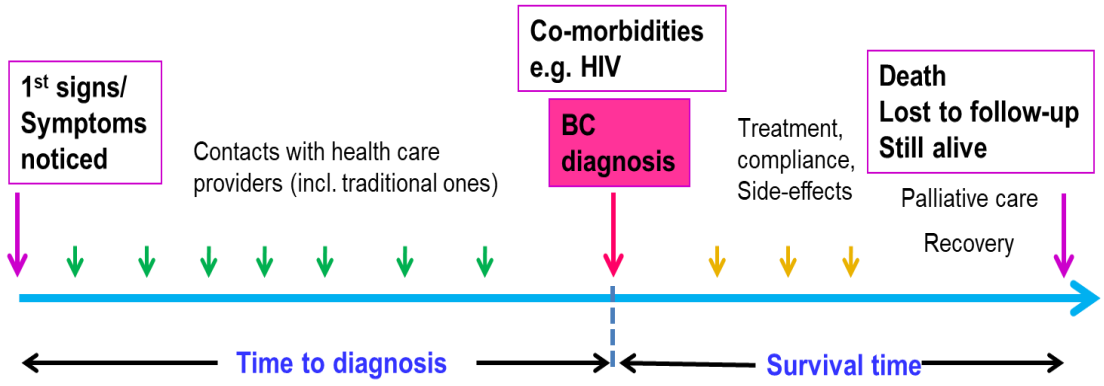

Figure 3.2 Conceptual framework for the ABC-DO study

Funded by the Susan G. Komen and US National Cancer Institutes, the ABC-DO study aims to:

- To measure survival rates for breast cancer patients across public hospitals in different African settings.
- To identify determinants of breast cancer survival that account for within-setting, between-woman survival differences, and for between-setting differences. Proximal determinants include stage, tumour biology, treatment received, age, anthropometry, and co-morbidities. Distal factors include socioeconomic status, culture, and health care access and beliefs.
- To identify context-specific factors that can be targeted to improve breast cancer survival most effectively in Africa.
- To dissect the entire time-specified journey of a breast cancer patient, from pre-diagnosis onwards to identify therapy components and their delays that influence breast cancer survival.
- To implement active follow-up after breast cancer diagnosis with low losses to follow-up using mobile phones and real-time m-Health technologies for data collection.

3.3.1 Study design and setting

A prospective hospital-based cohort of women newly diagnosed with primary breast cancer at eight oncology centres in five sub-Saharan African countries. These countries include Southern Africa (Namibia, South Africa, and Zambia) where HIV prevalence is high, East Africa (Uganda) where HIV prevalence is intermediate and West Africa (Nigeria) where HIV prevalence is low (Figure 3.3). The study is led by the International Agency for Research on Cancer (IARC) and the London School of Hygiene and Tropical Medicine (LSHTM). The participating countries and hospitals (Table 3.1) were not only chosen because of their already established collaborations with IARC/LSHTM but also their diversity in terms of their diverse catchment populations (regional vs. national), breast cancer incidence, HIV prevalence, healthcare systems and treatment availability.

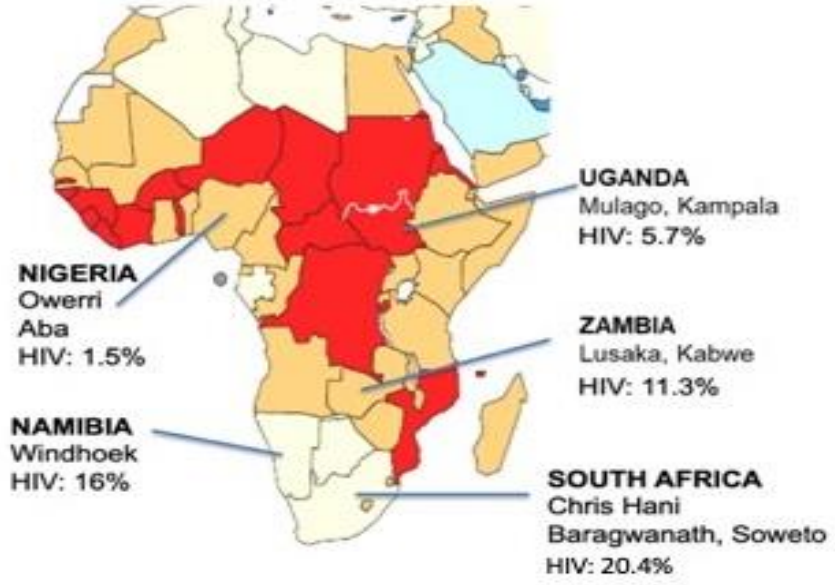

Figure 3.3 Map showing ABC-DO participating countries/cities and respective national HIV prevalence estimates.

Table 3.1 Characteristics of participating hospitals and number of HIV-infected women in ABC-DO study

					Receptor determination and therapies available: Y=yes, N=no, R=upon referral				
	Recruitment dates (MM/YY)	**Catchment population**	**No. women**	**No. women with HIV (%)**	**ER, PR, HER2 (%)**	**Surgery**	**Chemotherapy**	**Radiotherapy**	**Hormonal**	**Trastuzumab**
S.Africa, Chris Hani Baragwanath	01/15-06/17	Soweto	632	167 (26)	100	Y	Y	Y	Y	N
Namibia, Windhoek Central Hospital	09/14-10/16	National	481	60 (12)	100	Y	Y	Y	Y	Y
Uganda, Mulago Hospital, Kampala	12/14-03/17	National	421	57 (14)	10	Y	Y	N	Y	N
Zambia, Lusaka[3]	05/16-05-17	National, regional	198	36 (18)	N	Y	Y	N	Y	N
Nigeria, Owerii[1], Aba[2]	10/14-03/17	State-wide	386	12 (3)	N	Y	Y	R	Y	N
All			2154	332						

1 Federal Medical Centre Owerri; Abia State University Teaching Hospital and Maranatha hospital (private); 3 Cancer Diseases Hospital and breast camp at Kabwe General Hospital

3.3.2 Participant recruitment

Between September 2014 and December 2017, all women newly diagnosed with breast cancer were invited to participate in the study. Women were eligible for inclusion if they were 18 years or older, had a confirmed primary breast cancer (histopathological/cytological/clinical diagnosis) and were being newly seen at the participating hospital[9]. A total of 2,313 women were recruited into the study, of whom 159 were excluded leaving a total of 2,154 women including 332 who were also HIV positive (Table 3.3). Reasons for exclusion included not having breast cancer (85 women), being previously treated for breast cancer or recurrence (54) or being from small racial groups or having no adequate follow-up information (20). Participants answered a face-to-face baseline interview, consented to researchers having access of their medical records and tumour tissue specimens, and to be actively followed up via 3-monthly telephone interviews[9-11].

At baseline, women were asked about their pre-diagnostic experience including the dates they first noticed their symptoms and of subsequent contacts with formal and informal (e.g., traditional healers) healthcare providers; their breast cancer knowledge, health attitudes and cultural beliefs; information on breast cancer risk factors; and socioeconomic status. Standard proformas were used to extract clinical, pathological and treatment information from hospital records, including information on the breast lesion - i.e., stage, grade, cytology/histology, grade, and tumour receptor status (where available). Captured data from clinical records also included treatment recommended/received, dates of treatment initiation and completion, treatment type (surgery, chemo/hormonal/radiotherapy) and nature (e.g., drug names/combination, length, and frequency of dose, etc.) and adverse effects. Additional treatment-related data was obtained through patient self-reports at their 6-month follow-up telephone interview. Questions included whether they had received treatment, its type, and reasons if treatment was not received or completed.

3.3.3 HIV data in ABC-DO study

The ABC-DO study is a generic breast cancer cohort rather than an HIV-focused one. As such, HIV testing was not part of the study protocol. However, HIV status and other HIV-related data were captured at the baseline interview. In South Africa, all consenting women were tested for HIV. Elsewhere, HIV status was woman-self-reported during the baseline interview and during the administration of presenting symptoms questionnaire (with a median of 31 days IQR 6-113 between the two self-reports). For this thesis, a

woman was considered HIV-positive at breast cancer diagnosis if either of these were positive. A total of 169 women (from Nigeria, Namibia, Uganda, and Zambia) self-reported to be HIV positive at least once - 130 (77%) had concordant HIV-self-report in both questionnaires, 20 (12%) had a HIV-positive self-report recorded in their presenting symptoms questionnaire only, and 19 (11%) in the baseline interview only. Information on ART, CD4 and HIV-RNA was also collected.

3.3.4 Study implementation

ABC-DO study protocol was implemented using a specifically designed and customized mHealth application developed by Mobenzi Technologies (Pty) – a South African mHealth Solutions company that develops and supports mobile applications for health research. Further details about the application are outlined in the published ABC-DO protocol[9]. Follow-up of participants was done actively through 3-monthly telephone calls to the woman or her next-of-kin. All data collection, study data management and quality assurances were done through this application, which was installed on research assistant (RA)'s mobile phones/tablets (with exception of South Africa site where an already existing electronic database is used). The mHealth application allowed study data to be available in real time, remote real-time monitoring of fieldwork progress, and automatic generation of daily 'to do' lists for the RAs (e.g., patients to be called, data to be extracted from clinical records, e.g., pathology results).

The technology was pivotal in minimizing losses to follow-up (by five times less), overcoming a serious limitation of previous breast cancer survival studies in SSA. The application helps RAs to maintain regular contact with women who did not return to hospital through the regular follow-up prompts. The regular contact with woman's next of kin also ensured researchers of being informed about the patient's death in cases where the hospital was not aware of it.

3.3.5 Relevance to the PhD, strengths, and limitations

The ABC-DO study is one of the largest breast cancer cohorts in SSA, with a considerable proportion of women living with HIV. The study provides a unique within-Africa cross-country perspective. The five countries included in ABC-DO have a wide geographical spread of population (Western, Eastern, Central and Southern Africa), and are diverse in terms of HIV prevalence, health systems and demographic-, economic- and even breast cancer epidemiology transition. The detailed epidemiological data collected on the entire breast cancer journey enable comprehensive examination of the

role of HIV status on patient pathways to breast cancer presentation, diagnosis and treatment initiation and survival. The study used an mHealth application for study management and standardisation of data collection in real-time. This has enhanced data quality and completeness and minimized losses to follow-up.

However, there some limitations that need to be considered. ABC-DO is a hospital-based study, hence women who seek care elsewhere may have been missed. Most of the participating hospitals are referral centres at the top tier in referral hierarchy of a given country inherently excluding other types of women e.g., those who may not afford transport/accommodation costs. The pre-diagnostic history is self-reported and therefore, prone to recall bias i.e., HIV-positive patients may recall events leading to their diagnosis differently from HIV-negative counterparts.

HIV data from some of ABC-DO study sites (except South Africa) were largely self-reported. As such there is potential for misclassification of HIV status as some women might have misreported. Additionally, other HIV-related data (e.g., CD4 count, ART use and viral load) from these sites are largely missing. However, HIV testing is clinically routine and detailed information on HIV-positive patients such as CD4 count, viral load, HIV treatment and duration were captured in South Africa. Analyses restricted to tested HIV status data, and sensitivity analyses were carried out in this thesis (as detailed in chapter 6) to assess the extent and implication of such potential misclassification.

3.4 UNAIDS Mortality estimates

The United Nations Joint Programme on HIV/AIDS (UNAIDS) publishes annually updated estimates of the global HIV epidemic. These estimates, developed by partner countries with support from UNAIDS, are critical for describing the current state of the AIDS epidemic at local, national, regional and global level[12]. The UNAIDS, through the UNAIDS Reference Group on Estimates, Modelling and Projections, developed statistical and mathematical tools, in a software called Spectrum, which are used to model the HIV epidemic and generate annual estimates[13-15]. Almost all countries use this software to develop their national and sub-national estimates of HIV-related key indicators including HIV prevalence and incidence, and AIDS-related mortality[16,17].

Within the Spectrum software is an Estimation and Projection Package which uses surveillance and survey data (from sources such as antenatal care and routine Prevention of Mother-To-Child Transmission (PMTCT) programs), to estimate trends in HIV prevalence, incidence and to determine consequences of these projections,

including number of people living with HIV by age and sex, new infections, and AIDS deaths. Detailed descriptions of the software and modelling tools employed are available in dedicated publications by Stover et. al.[14,15].

This data source was used to obtain national female age-specific mortality rates, by HIV status, for the countries where ABC-DO study was implemented.

3.4.1 Relevance of the data source to the PhD

The reported lower survival rates after a breast cancer diagnosis in HIV-infected women compared to their HIV-uninfected counterparts with breast cancer may be due to the higher background mortality associated with HIV/AIDS. However, few studies[18-20], all from the USA, have examined breast cancer-specific mortality in HIV-infected women compared to HIV-uninfected women i.e. taking into account the difference in background mortality between the two groups. There have been no similar studies conducted in sub-Saharan Africa (SSA) yet, probably due to lack of accurate cause of death information. Generally, such studies would require well-functioning civil registration and vital statistics systems with a high level of coverage and good enough quality of cause of deaths information. Very few countries in SSA have such systems in place rendering it difficult to conduct any cause-specific survival analyses.

In the absence of good quality information on cause of death, alternative statistical methods e.g., relative survival methods can be used to achieve similar (but not identical) results. Relative survival methods estimate excess mortality rate as a difference between all-cause mortality rate among the patients and the expected mortality rate of a comparable group in the general population[21,22]. As such, these methods do not require cause of death information as they use total mortality experience including that of the disease under study. Relative survival, therefore, is calculated as overall observed survival for patients with a given condition/disease divided by expected survival of a similar population without the disease[21,22];

Relative (net) survival (breast cancer patients) =

$$\frac{\textit{Overall observed survival (breast cancer patients)}}{\textit{Expected survival (similar population without breast cancer, in general population)}}$$

The expected survival is estimated from national life tables. Lifetables provide information on estimated sex- and age-specific death rates for a particular population and time period based on records from vital registration systems. Thus, in HICs, national

life tables can easily be calculated due to presence of robust vital registration systems. On the other hand, in SSA where similar systems are often not adequately available, national life tables for countries in SSA, produced by institutions such as the WHO and the Institute for Health Metrics and Evaluation, are based on estimated sex- and age-specific death rates rather than observed death rates.

For this PhD, comparing relative survival after breast cancer diagnosis between HIV-infected and HIV-uninfected women, therefore, requires national life tables separated by HIV status, to properly adjust for differences in background mortality due to HIV/AIDS. Sadly, to date, there have no published national life tables by HIV status in SSA despite the huge burden in the region. Therefore, the UNAIDS HIV mortality estimates for countries participating in the ABC-DO study have been used in this thesis to generate national life tables by age, sex, and HIV status. The resulting life tables have been used in relative survival methods to estimate breast cancer net survival in HIV-infected women compared with HIV-uninfected women.

As with all modelling exercises, these estimates are not without limitations. The sources of data fed into these models may be limited in some countries. For example, countries with generalized HIV epidemics such as in SSA (i.e. countries where HIV is firmly established in the general population) estimates of HIV prevalence are predominantly based on surveillance among pregnant women attending sentinel antenatal clinics hence limited to women aged 15-49[16,23]. Such estimates may not well represent the HIV trends in older women and men. However, in the absence of robust vital registration systems, these estimates remain the best one can hope for.

3.5 Summary

- In this chapter, I have described three data sources used to address the research aims of this thesis: Karonga HDSS (chapter 4); ABC-DO study (chapter 5-7); and UNAIDS mortality data (chapter 7).
- The Karonga HDSS was established to collect epidemiological data, particularly on HIV, on a longitudinal basis. It provided data to assess the validity of self-reported HIV status. The HDSS is a rich resource based on large longitudinal HIV data that has been collected for over 10 years. Although not part of ABC-DO study i.e., results may not be generalisable to ABC-DO study sites, Karonga HDSS setting is similar to ABC-DO study sites. Thus, results from this analysis may to some extent be extrapolated to ABC-DO study sites.

- The ABC-DO study is one of the largest breast cancer cohorts in Africa, recruiting patients from five African countries with varied HIV prevalence, patient profiles and healthcare systems. The use of mHealth for study management and standardised collection of data in real-time ensured that missing data are minimal and losses-to-follow-up (one of key issues in prospective studies in SSA) are reduced.
- One of limitations of ABC-DO study for this thesis is that HIV status and related data were self-reported in most ABC-DO study sites except in South Africa where HIV testing was done.
- UNAIDS mortality data are annually updated estimates of global HIV epidemic. These are produced by UNAIDS and partner countries to gauge the state of the HIV epidemic. They include HIV prevalence, treatment coverage and mortality estimates both in HIV-infected and HIV-uninfected population. They provide a source for generating HIV-specific life tables. Although based on prediction models that have been validated and used for a long time, the sources of data that feed into these models may be limited.

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Chapter 4 Accuracy and validity of self-reported HIV status

4.1 Introduction

In this chapter, I assess the accuracy and validity of self-reported HIV status information and associated factors, using data from the Karonga HDSS in northern Malawi (describe in chapter 3), a setting similar to ABC-DO settings. Results from this study are presented as research paper 1 which was published in AIDS journal.

As stipulated in the previous chapter, the ABC-DO study is a general breast cancer cohort rather than a HIV-focused one. Most of the HIV-status and HIV-related data were self-reported either at recruitment or during the first symptoms questionnaire except in South Africa where routine HIV testing was done. In this chapter, I therefore, assessed accuracy of and factors that influence accurate reporting of a HIV-positive status in a population of individuals who were tested and were informed of their HIV status. To examine the validity of self-reported HIV status, I compared self-reported HIV status with biomarker-confirmed HIV test status overall and by socio-demographic characteristics and settings in which self-reported HIV status was obtained, to identify factors associated with accurate self-reporting of HIV status.

4.2 Research paper 1

Assessing the validity of and factors that influence accurate self-reporting of HIV status after testing: a population-based study.

(https://journals.lww.com/aidsonline/fulltext/2020/05010/assessing_the_validity_of_and_factors_that.14.aspx)

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed <u>for each</u> research paper included within a thesis.

SECTION A – Student Details

Student ID Number	LSH396778	**Title**	Mr.
First Name(s)	Steady Jerome Dickson		
Surname/Family Name	Chasimpha		
Thesis Title	Breast cancer in women living with HIV in Sub-Saharan Africa: presentation, diagnosis, and survival		
Primary Supervisor	Prof. Isabel dos-Santos-Silva		

If the Research Paper has previously been published, please complete Section B, if not please move to Section C.

<u>SECTION B – Paper already published</u>

Where was the work published?	AIDS Journal		
When was the work published?	30 January 2020		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
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<u>SECTION D – Multi-authored work</u>

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the first and corresponding author on this paper. I developed the analytical plan and led the statistical analysis with contributions from co-authors JG, IdSS, VM and EM. JG, one of the co-PIs of the original cohort, helped with the analytical plan, variable selection, and facilitated the data extraction for my analyses. AD contributed to data collection. I wrote the first draft of the manuscript and revised it based on comments from all co-authors and peer-reviewers.

SECTION E

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Date	21 October 2023

OPEN

Assessing the validity of and factors that influence accurate self-reporting of HIV status after testing: a population-based study

Steady J.D. Chasimpha[a], Estelle M. Mclean[a], Albert Dube[a,b], Valerie McCormack[a,c], Isabel dos-Santos-Silva[a] and Judith R. Glynn[a]

Objectives: To assess the validity of self-reported HIV status, and investigate factors that influence accurate reporting of HIV-positive status, in a population tested and informed of their HIV test result.

Design: Prospective cohort study.

Methods: We compared self-reported HIV status with biomarker-confirmed HIV test status among participants of Karonga Health and Demographic Surveillance Site in rural northern Malawi. We linked information on HIV test results to subsequent self-reported HIV status, and calculated sensitivity, specificity, positive predictive value and negative predictive value for self-reported HIV status (considered as a diagnostic test). We used Poisson regression with robust variance estimators to examine predictors of accurate self-reporting of HIV-positive status.

Results: Among 17 445 adults who tested for HIV, were recorded as having received their HIV test results, and had a subsequent self-reported HIV status between 2007 and 2018: positive predictive value of self-reported HIV status was 98.0% (95% confidence interval: 97.3–98.7); negative predictive value was 98.3 (98.1–98.5); sensitivity was 86.1% (84.5–87.7); and specificity was 99.8% (99.7–99.9). Among true HIV-positive people, those who were younger, interviewed in community settings, and had tested for HIV longer ago were more likely to misreport their HIV-positive status.

Conclusion: In this setting, self-report provides good estimates of test-detected HIV prevalence, suggesting that it can be used when HIV test results are not available. Despite frequent HIV testing, younger people and those interviewed in community settings were less likely to accurately report their HIV-positive status. More research on barriers to self-reporting of HIV status is needed in these subgroups.

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AIDS 2020, **34**:931–941

Keywords: HIV status, Malawi, self-report, sub-Saharan Africa, validity

Introduction

With the wide availability of HIV-testing, many people already know their HIV status and may be reluctant to retest for research studies. Self-reported HIV status may be used, but participants may misreport. This may be for fear of stigma and discrimination [1] or when they feel that there are incentives and/or extra support services associated with a particular HIV status [2]. For example, reporting to be HIV-positive anticipating customized care or HIV-negative to be recruited into studies.

Despite self-report being a useful source of HIV data, its validity has not been well characterized. Most prior

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Received: 2 November 2019; revised: 29 January 2020; accepted: 10 February 2020.

DOI:10.1097/QAD.0000000000002513

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studies on self-reported HIV status in sub-Saharan Africa (SSA) focused on people's perception of their likelihood of HIV infection and actual HIV test results [2,3]. There are few studies that compared self-reported HIV data against HIV test results in SSA. In a South African study in older adults, concordance between self-reported HIV status and serology was very high among seronegative people (specificity 98.4%), but low among seropositive people (sensitivity 66.2%) [4]. As HIV self-reports preceded the HIV test, the study included individuals who did not know their HIV status. However, restricting to only those who knew their status did not improve sensitivity estimates. Among people who reported knowing their HIV status in demographic surveys in Malawi (2010) and Uganda (2011), agreement between self-reported HIV status and test-detected HIV status was even lower (26.1–44.2%) [5]. In the 2012 Kenya AIDS Indicator survey, sensitivity for self-reported HIV status was 47% [6].

As access to HIV testing and counselling services continue to expand, more people will become aware of their HIV status. This poses challenges on willingness to participate in HIV testing especially for individuals who already know their HIV-positive status [7]. Here, we assess the validity of self-reported HIV status among adults (aged 15 and above) who had been tested and informed of their test results, using systematically collected prospective data from Karonga Health and Demographic Surveillance Site (HDSS) in rural northern Malawi. We compare performance of self-reported HIV status between community and clinic settings. We focus on sensitivity rather than specificity, to examine factors that influence accurate reporting of an HIV-positive status.

Methods

Study setting and population

We used population-based cohort study data on HIV test results and subsequent HIV self-reports collected by the Malawi Epidemiology and Intervention Research Unit (MEIRU, formerly known as the Karonga Prevention Study). Apart from conducting population-based epidemiological studies, MEIRU also runs the Karonga HDSS [8]. The HDSS was established in 2002 in rural northern district of Malawi, routinely collecting information on births, deaths (monthly) and migrations (annually). Regular community-wide surveys are conducted to capture information on socio-economic status, monitor HIV-infection patterns and evaluate impact of interventions carried out in the area. There are now over 40 000 people in the HDSS, most of whom are rural subsistence farmers, fishermen and small traders [9].

HIV data

Following a sample serosurvey completed between 2005 and 2006 [7,10], HIV data in the HDSS are available mainly through regular population-wide house-to-house cross-sectional serosurveys. By 2011, a total of four such surveys had been conducted using different types of rapid HIV tests [10]. In addition, HIV testing is offered in clinics and research studies [7]. Self-reported data on previous HIV testing, approximate date, and result of most recent HIV test are collected at the time of HIV testing. Consenting participants may choose not to be informed of their HIV test results. HIV testing is also available from service providers within and outside the HDSS.

We used the participant unique identification number and dates to link all HIV test results to corresponding data on subsequent self-reported HIV status, and created record pairs between the HIV test and self-reported HIV status. As such we had multiple records of HIV test results and subsequent self-reports per individual. For simplicity, and to get the most contemporaneous results, we analysed the most recent pair of an HIV test and its subsequent self-reported HIV status in individuals who chose to receive, and were given their results.

Socio-economic and demographic data

Socio-economic and demographic data in Karonga HDSS are usually updated during the annual HDSS surveys. These include marital status, level of education, and occupation. Using occupation and reliability of income, we created an employment score as an indicator of socio-economic status, in which low is the least skilled/reliable (e.g. piece work) and high is the most skilled/reliable (e.g. government worker paid monthly). The medium category consists of predominantly self-employed subsistence farmers. We assessed area of residence using distance between participants' residence and the tarmac road [10,11].

Statistical analysis

We restricted the analysis to adults aged 15 years and above, and calculated true HIV prevalence, as assessed by the rapid HIV tests, in each category of self-reported HIV status (negative, positive, don't know, refuse to disclose and never tested) according to whether participants received their HIV test result. Using Pearson's chi-squared test, we assessed distribution of participants' socio-demographic characteristics by self-reported HIV status, recorded as positive, negative and unknown (the latter included individuals who reported 'don't know,' 'refuse to disclose' and 'never tested'). We then assessed performance of self-reported HIV status against serological HIV test result obtained from the rapid HIV tests – regarded here as the 'gold-standard'.

Restricting to individuals who were recorded as having received their test results, and who self-reported being either HIV-positive or HIV-negative (i.e. excluding those who self-reported HIV-unknown status) we estimated [with their 95% confidence intervals (CIs)]:

(1) Sensitivity: Probability of self-reporting HIV-positive among those who tested HIV-positive.
(2) Specificity: Probability of self-reporting HIV-negative among those who tested HIV-negative.
(3) Positive predictive value (PPV): Probability of testing HIV-positive among those who self-reported HIV-positive.
(4) Negative predictive value (NPV): Probability of testing HIV-negative among those who self-reported HIV negative [12,13].

Changes in sensitivity and specificity by time between the HIV test and the self-report were assessed.

We also examined factors associated with the accuracy of self-reported HIV status. Only serologically HIV-positive individuals who were known to have received their HIV test results were included in this analysis. The outcome was binary (yes or no) for accurately reporting being HIV-positive. We used Pearson's chi-squared test for equality of proportions between populations, to identify variables associated with accurate reporting of HIV-positive status at P value less than 0.2, for assessment in multivariable models. Because of a high proportion reporting HIV-positive, we estimated prevalence ratios rather than odds ratios as a measure of association, using modified Poisson regression models (with robust variance estimators). Robust variance estimators were used to correct for wider CIs that would be observed in regular Poisson models [14,15]. The basic model included age, sex and calendar year of HIV self-report *a priori*. Other variables were added one at a time to choose a parsimonious yet best fitting model.

For those who had more than one pair of self-reports followed by test results, we compared the first pair with the most recent pair to see if there were changes in self-reporting (whether accuracy improved) in individuals who had retested. We used Stata 16 (StataCorp, College Station, Texas, USA) and R-software (R Development Core Team 2019, Vienna, Austria) for analyses and graphics, respectively.

Ethics

Ethical approval for demographic surveillance and HIV studies in Karonga HDSS area were obtained from the Malawi National Health Sciences Research Committee (approval #s NHSRC/01/38 and 419), and the research ethics committee of London School of Hygiene & Tropical Medicine (# 5081). For this analysis, additional approval was obtained from the London School of Hygiene & Tropical Medicine ethics committee (#16495).

Results

Between 2007 and 2018, 17 856 adults were tested for HIV and had a subsequent self-reported HIV status. Of these, 10 148 (56.8%) were women and 7709 (43.2%) were men. Median age was 31.5 years (interquartile range: 22.7–44.2). Nearly all participants [17 445 (97.7%)] received their HIV test results, with just 145 (0.8%) individuals choosing not to know their HIV test results, and 266 (1.5%) with missing data on receipt of HIV test results. Overall, there were 2046 (11.5%) HIV-infected people. HIV prevalence was higher among women (12.1%) than men (10.6%). Self-reported data on current antiretroviral therapy (ART) use was available for 1423 (69.5%) of all individuals with an HIV-positive test. Of these, 1171 (82.3%) reported to be on ART. ART data were missing/unknown for 623 (30.5%) of all HIV-positive individuals.

Among those who had received their HIV test results: true HIV prevalence was 98.0% in individuals who self-reported as HIV-positive (i.e. the PPV); 1.6% among self-reported HIV-negatives; 42.0% among those self-reporting not knowing; 36.2% among those refusing to disclose; and 12.4% among those self-reporting to have never been tested (Fig. 1).

Self-reported HIV prevalence

Table 1 shows participant characteristics by self-reported HIV status. Overall self-reported HIV prevalence (excluding those who reported 'unknown') was 9.6%, whereas the serological HIV prevalence in the same individuals was 11.5%.

Performance of self-reported HIV status among those who were recorded as having received their results

The joint distribution of self-reported and true HIV status among the 17 148 participants who received their results and had valid self-reported HIV status (i.e. excluding those self-reporting 'unknown'), was 89.0% true negatives, 9.3% true positives, 0.2% false positives and 1.5% false negatives that is, discordant pairs were predominantly of HIV-positive individuals reporting as HIV-negative, whereas it was rare for an HIV-negative individual to report being HIV-positive.

The overall sensitivity for self-reported HIV status was 86.4% (95% CI: 84.8–88.0%) and specificity was 99.8% (99.7–99.9%). PPV and NPV were also high 98.0% (97.3–98.7%) and 98.4% (98.2–98.6%), respectively, (Table 2). The estimates were similar when all participants were considered (i.e. regardless of whether individuals were recorded to have received their HIV test result): sensitivity was 86.2% (84.6–87.7) and specificity was 99.8 (99.7–99.9). PPV and NPV were 98.1% (97.3–98.7) and 98.3% (98.1–98.5), respectively.

Both sensitivity and PPV increased with age: sensitivity was 65.5% in 15–24 year olds compared with 91.9% in those aged 45 years and over. Individuals who had never married had lower sensitivity of self-reported HIV status (75.6%; 60.5–87.1%) than those currently (84.8%; 82.5–86.6%) or previously married (89.3%; 86.2–91.9%).

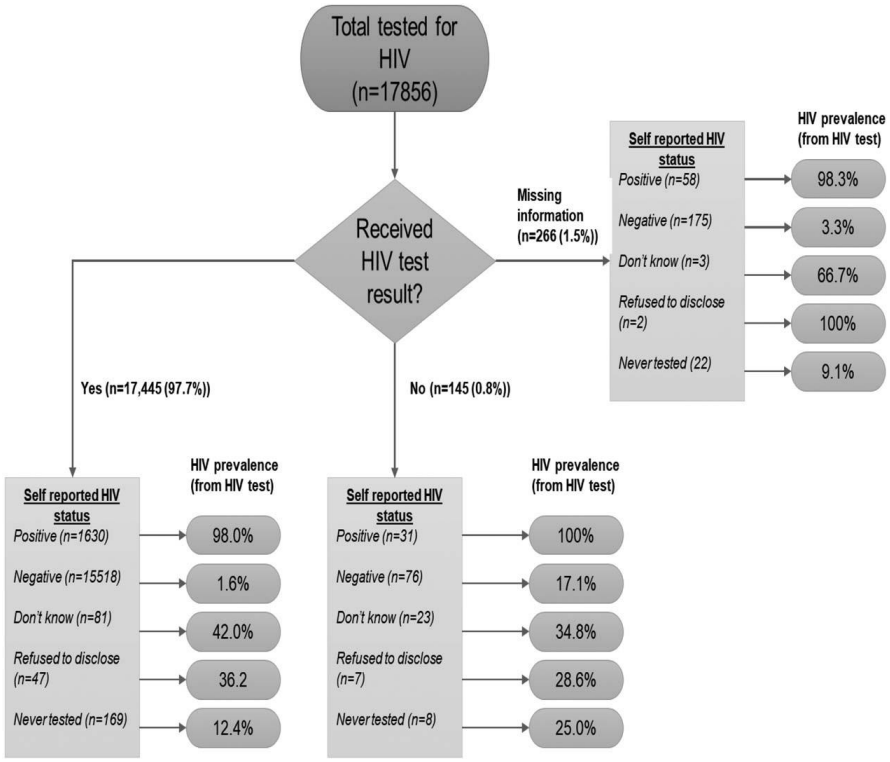

Fig. 1. HIV prevalence and self-reported HIV status according to whether participants received their HIV test results.

Sensitivity and PPV were slightly higher for self-reported HIV status conducted in clinic settings [92.2% (89.3–94.3%) and 99.1% (97.7–99.8%, respectively] compared with community settings [84.4% (82.0–85.9%) and 97.6% (96.6–98.4%), respectively; Table 2].

The longer the duration between HIV testing and self-reported HIV interview, the lower the sensitivity and PPV for self-reported HIV status. Sensitivity was 94.3% (91.2–96.5%) among those reporting within six months of HIV testing compared with 76.1% (69.6–81.9) among those self-reporting 2–4 years after the test. Overall, specificity was similar and very high (>99%) across all levels of socio-demographic factors except for those with an interval of 60 months or more (97.6%).

Figure 2 shows plots of sensitivity and specificity of self-reported HIV status and time since most recent HIV test by sex, setting and calendar period. For the decline in sensitivity with increasing time since most recent HIV test, the pattern was similar for males and females, but differed by setting, with sensitivity in clinic settings remaining higher than in community settings.

Sensitivity decreased with increasing time since most recent HIV across all calendar periods (in which self-reported HIV status was collected), but was markedly lower in the earlier period (2007–2010) than in latter periods (2011–2012 and 2013–2018). However, there were no self-reports beyond 5+ years in earlier periods. Overall, specificity remained high (near 100%) regardless of length of the time interval between HIV testing and self-reporting (Fig. 2).

There were 8076 individuals with at least two pairs of self-report and HIV test result. This included 47 (0.6%) individuals who seroconverted between tests, of whom 26 (55.3%) reported their new HIV-positive status accurately (Supplementary Table 1, http://links.lww.com/QAD/B690). Excluding those who seroconverted, self-reported HIV status was consistent (i.e. correct in both) in 7939 (98.8%) individuals. Among 446 HIV-

Table 2. Performance of HIV self-report against serological HIV test among 17 148 individuals who received their HIV test results.

Characteristic	Description	Total	True positives	False negatives	False positives	PPV[a] (95% CI[c])	NVP[b] (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Overall		17 148[d]	1598	251	32	98.0 (97.2–98.7)	98.4 (98.2–98.6)	86.4 (84.8–88.0)	99.8 (99.7–99.9)
Sex	Female	9758	959	153	18	98.2 (97.1–98.9)	98.3 (98.0–98.5)	86.2 (84.1–88.2)	99.8 (99.7–99.9)
	Male	7390	639	98	14	97.9 (96.4–98.8)	98.5 (98.2–98.8)	86.7 (84.0–89.1)	99.8 (99.6–99.9)
Age group	15–24	5484	57	30	9	86.4 (75.7–93.6)	99.4 (99.2–99.6)	65.5 (54.6–75.4)	99.8 (99.7–99.9)
	25–34	4613	443	106	10	97.8 (96.0–98.9)	97.5 (96.9–97.9)	80.7 (77.1–83.9)	99.8 (99.5–99.9)
	35–44	2960	596	71	4	99.3 (98.3–99.8)	97.0 (96.2–97.6)	89.4 (86.8–91.6)	99.8 (99.6–100)
	45+	4091	502	44	9	98.2 (96.7–99.2)	98.8 (98.4–99.1)	91.9 (89.3–94.1)	99.7 (99.5–99.9)
Marital status	Never	2446	34	11	6	85.0 (70.2–94.3)	99.5 (99.2–99.8)	75.6 (60.5–87.1)	99.8 (99.5–99.9)
	Currently married	10 815	940	169	16	98.3 (97.3–99.0)	98.3 (98.0–98.5)	84.8 (82.5–86.8)	99.8 (99.7–99.9)
	Previously married	1544	435	52	7	98.4 (96.8–99.4)	95.3 (93.9–96.5)	89.3 (86.2–91.9)	99.3 (98.6–99.7)
	Unknown	2343	189	19	3	98.4 (95.5–99.7)	99.1 (98.6–99.5)	90.9 (86.1–94.4)	99.9 (99.6–100)
Formal education	None	641	63	4	1	98.4 (91.6–100)	99.3 (98.2–99.8)	94.0 (85.4–98.3)	99.8 (99.0–100)
	Incomplete primary	6947	571	83	11	98.1 (96.6–99.1)	98.7 (98.4–99.0)	87.3 (84.5–89.8)	99.8 (99.7–99.9)
	Complete primary	4535	468	71	8	98.3 (96.7–99.3)	98.3 (97.8–98.6)	86.8 (83.7–89.6)	99.8 (99.6–99.9)
	Secondary/higher	4871	480	90	7	98.6 (97.1–99.4)	97.9 (97.5–98.3)	84.2 (81.0–87.1)	99.8 (99.7–99.9)
Rank of employment in last 2 years[e]	Low	3604	109	17	7	94.0 (88.0–97.5)	99.5 (99.2–99.7)	86.5 (79.3–91.9)	99.8 (99.6–99.9)
	Medium	11 809	1113	186	17	98.5 (97.6–99.1)	98.3 (98.0–98.5)	85.7 (83.7–87.5)	99.8 (99.7–99.9)
	High	1618	360	44	3	99.2 (97.6–99.8)	96.5 (95.3–97.4)	89.1 (85.7–92.0)	99.8 (99.3–99.9)
Occupation in last 2 years	Not working	3491	82	13	7	92.1 (84.5–96.8)	99.6 (99.3–99.8)	86.3 (77.7–92.5)	99.8 (99.6–99.9)
	Farming	11 067	1002	165	16	98.4 (97.5–99.1)	98.4 (98.1–9806)	85.9 (83.7–87.8)	99.8 (99.7–99.9)
	Professional	1039	197	24	2	99.0 (96.4–99.9)	97.1 (95.8–98.2)	89.1 (84.3–92.9)	99.8 (99.1–100)
	Other	1434	301	45	2	99.3 (97.6–99.9)	96.0 (94.7–97.1)	87.0 (83.0–90.4)	99.8 (99.3–100)
Distance to main road in km	<1 km	7934	945	129	16	98.3 (97.3–99.0)	98.2 (97.8–98.5)	88.0 (85.9–89.9)	99.8 (99.6–99.9)
	1–4.99 km	5696	481	81	9	98.2 (96.5–99.2)	98.4 (98.1–98.8)	85.6 (82.4–88.4)	99.8 (99.7–99.9)
	5+ km	3387	160	37	4	97.6 (93.9–99.3)	98.9 (98.4–99.2)	81.2 (75.1–86.4)	99.9 (99.7–100)
Time since HIV test	<6 months	1452	313	19	3	99.1 (97.3–99.8)	98.3 (97.4–99.0)	94.3 (91.2–96.5)	99.7 (99.2–99.9)
	6–11 months	4282	488	67	7	98.6 (97.1–99.4)	98.2 (97.7–98.6)	87.9 984.9–90.5)	99.8 (99.6–99.9)
	12–23 months	9114	615	108	8	98.7 (97.5–99.4)	98.7 (98.5–99.0)	85.1 (82.3–87.6)	99.9 (99.8–100)
	24–59 months	2011	150	47	8	94.9 (90.3–97.8)	97.5 (96.6–98.1)	76.1 (69.6–81.9)	99.6 (99.1–99.8)
	60+ months	289	32	10	6	84.2 (68.7–94.0)	96.0 (92.8–98.1)	76.2 (60.5–87.9)	97.6 (94.8–99.1)
Calendar year of self-reported HIV status	2007–2010	5567	596	123	7	98.8 (97.6–99.5)	97.5 (97.1–97.9)	82.9 (79.9–85.6)	99.9 (99.7–99.9)
	2011–2012	7512	624	62	11	98.3 (96.9–99.1)	99.1 (98.8–99.3)	91.0 (88.6–93.0)	99.8 (99.7–99.9)
	2013–2018	4069	378	66	14	96.4 (94.1–98.0)	98.2 (97.7–98.6)	85.1 (81.5–88.3)	99.6 (99.4–99.8)
Setting of HIV self-report	Community	15 022	1160	214	28	97.6 (96.6–98.4)	98.5 (98.2–98.7)	84.4 (82.4–86.3)	99.8 (99.7–99.9)
	Clinic	2126	438	37	4	99.1 (97.7–99.8)	97.8 (97.0–98.4)	92.2 (89.4–94.5)	99.8 (99.4–99.9)

[a]Positive predictive value.
[b]Negative predictive value.
[c]Confidence interval.
[d]Had received test results and self-reported HIV positive or negative that is all self-reported HIV unknown were excluded.
[e]Based on occupation and reliability of income. Low – least skilled/reliable; Medium – self-employed subsistence farmers; High – skilled and reliable for example professional government employee.

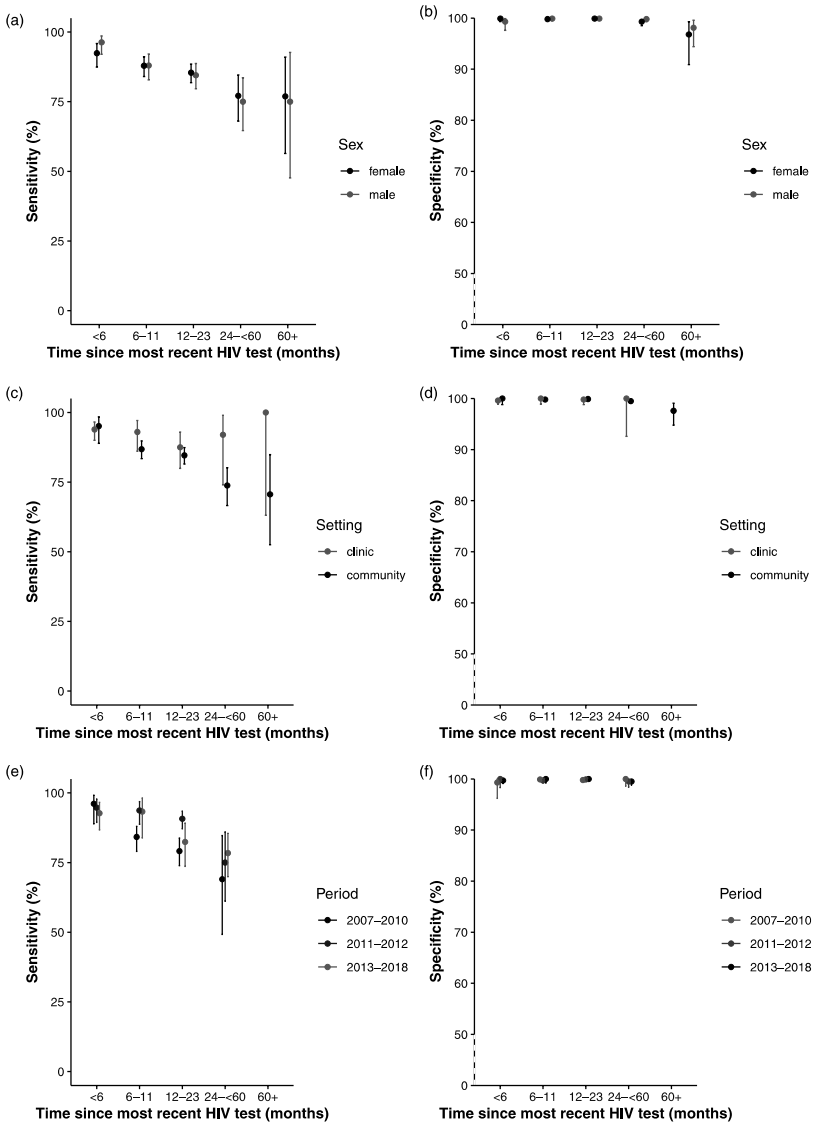

Fig. 2. Sensitivity and specificity of self-reported HIV by time since most recent HIV test, stratified by sex (a and b), and type of setting (c and d) and calendar year of self-report (e and f). *Note:* Estimates for clinic 60+ months in (d) not displayed because it was based on just nine records (specificity = 100%, 95% confidence interval: 2.5–100).

Table 3. Predictors of accurate reporting of HIV-positive status among HIV-infected individuals who received their HIV test results.

Characteristic	Description	Total, $N=1849$ N (col %)	Accurate reporting of HIV+ status: Yes N (row %)	No N (row %)	P value[a]	Crude PR[b] (95% CI)	Adjusted PR[c] (95% CI)	P value[d]
Sex	Female	1112 (60.1)	959 (86.2)	153 (13.8)		1	1	
	Male	737 (39.9)	639 (86.7)	98 (13.3)	0.7	1.01 (0.97–1.04)	0.99 (0.95–1.04)	0.8
Age at self-report	15–24	87 (4.7)	57 (65.5)	30 (34.5)		0.71 (0.61–0.83)	0.71 (0.61–0.83)	<0.001
	25–34	549 (29.7)	443 (80.7)	106 (19.3)		0.88 (0.84–0.92)	0.87 (0.83–0.91)	<0.001
	35–44	667 (36.1)	596 (89.4)	71 (10.6)		0.97 (0.94–1.01)	0.97 (0.93–1.00)	0.06
	45+	546 (29.5)	502 (91.9)	44 (8.1)	<0.001	1	1	
Marital status	Never	45 (2.4)	34 (75.6)	11 (24.4)		0.89 (0.75–1.05)	1.01 (0.86–1.20)	0.9
	Currently married	1109 (60.0)	940 (84.8)	169 (15.2)		1	1	
	Previously married	487 (26.3)	435 (89.3)	52 (10.7)		1.05 (1.01–1.10)	1.03 (0.99–1.07)	0.2
	Unknown	208 (11.3)	189 (90.9)	19 (9.1)	0.003	1.07 (1.2–1.13)	1.06 (1.00–1.11)	0.04
Highest formal education	None	67 (3.6)	63 (94.0)	4 (6.0)		1.08 (1.01–1.16)	1.01 (0.94–1.09)	0.8
	Incomplete primary	654 (35.7)	571 (87.3)	83 (12.7)		1	1	
	Complete primary	570 (31.2)	480 (84.2)	90 (15.8)		0.99 (0.95–1.04)	0.99 (0.95–1.03)	0.6
	Secondary/higher	539 (29.5)	468 (86.8)	71 (13.2)	0.1	0.96 (0.92–1.01)	0.98 (0.93–1.02)	0.3
Occupation in last 2 years	Not working	95 (5.2)	82 (86.3)	13 (13.7)		1.01 (0.92–1.09)		
	Farming	1167 (63.8)	1002 (85.9)	165 (14.1)		1		
	Professional	221 (12.1)	197 (89.1)	24 (10.9)		1.04 (0.99–1.09)	N/A	
	Other	346 (18.9)	301 (87.0)	45 (13.0)	0.6	1.01 (0.97–1.06)		
Rank of employment	Low	126 (6.9)	109 (86.5)	17 (13.5)		1.01 (0.94–1.09)		
	Medium	1299 (71.0)	1113 (85.7)	186 (14.3)		1	N/A	
	High	404 (22.1)	360 (89.1)	44 (10.9)	0.2	1.04 (1.00–1.08)		
Time since HIV test	<6 months	332 (18.0)	313 (94.3)	19 (5.7)		1	1	
	6–12 months	555 (30.0)	488 (87.9)	67 (12.1)		0.93 (0.90–0.97)	0.97 (0.93–1.01)	0.2
	12–24 months	723 (39.1)	615 (85.1)	108 (14.9)		0.90 (0.87–0.94)	0.92 (0.88–0.96)	<0.001
	24–60 months	197 (10.7)	150 (76.1)	47 (23.9)		0.81 (0.74–0.88)	0.83 (0.76–0.90)	<0.001
	60+ months	42 (2.2)	32 (76.2)	10 (23.8)	<0.001	0.81 (0.68–0.96)	0.81 (0.68–0.98)	0.03
Calendar year of self-reported HIV status	2007–2010	719 (38.9)	596 (82.9)	123 (17.1)		1	1	
	2011–2012	686 (37.1)	624 (91.0)	62 (9.0)		1.10 (1.05–1.14)	1.10 (1.06–1.15)	<0.001
	2013–2018	444 (24.0)	378 (85.1)	66 (14.9)	<0.001	1.03 (0.98–1.08)	1.04 (0.99–1.10)	0.2
Setting	Community	1374 (74.3)	1160 (84.4)	214 (15.6)		1	1	
	Clinic	475 (25.7)	438 (92.2)	37 (7.8)	<0.001	1.09 (1.06–1.13)	1.07 (1.02–1.11)	0.002
Distance to main road in km	<1 km	1074 (58.6)	945 (88.0)	129 (12.0)		1	1	
	1–4.99 km	562 (30.7)	481 (85.6)	81 (14.4)		0.97 (0.93–1.01)	0.98 (0.94–1.02)	0.3
	5+ km	197 (10.7)	139 (78.1)	39 (21.9)	0.03	0.88 (0.86–0.90)	0.94 (0.88–1.01)	0.09
Currently on ART[e]	No	235 (17.7)	225 (95.7)	10 (4.3)		1.01 (0.97–1.06)	N/A	
	Yes	1094 (82.3)	1065 (97.4)	29 (2.6)	0.2	1		

[a]Pearson's Chi-squared test of equal distributions.
[b]Prevalence ratio (PR) from univariate Poisson regression models with robust variance estimators for association between accurate reporting HIV+ and participants' characteristics.
[c]Multivariable Poisson regression Prevalence ratios adjusted for sex, age group, calendar period, marital status, formal education level, time since recent HIV test, setting and distance to main road.
[d]Wald's test P value.
[e]Antiretroviral therapy.

Shorter periods between HIV testing and self-reporting HIV status, were associated with correctly reporting being HIV-positive (chi-square test for trend: $P = 0.004$). HIV-infected individuals interviewed in clinic settings were more likely to accurately report their positive status than those in community settings (adjusted prevalence ratios: 1.07; 95% CI: 1.02–1.11) (Table 3).

Discussion

Understanding accuracy and determinants of correct reporting of HIV status is essential for HIV programs and epidemiological studies that may rely on self-reported HIV status data. In a large population-based study in rural northern Malawi of community members who had received an HIV test and been informed of the results, we found very high specificity, and high sensitivity for self-reported HIV status. We did find a small proportion (0.2%) of false positives – individuals self-reporting to be HIV-positive whose last known HIV result was negative, suggesting that our 'gold standard' HIV test database was extremely good but not perfect. These false positives were not surprising as HIV testing is available outside the study setting and such individuals may have tested positive elsewhere, a result not captured by the study. False positives were more common with large gaps between HIV testing and self-report, consistent with seroconversion after our last recorded test. Specificity and NPV were similar across different socio-demographic factors.

We observed higher PPV and sensitivity in older age groups compared with young ones. As shown in other studies, older people are more likely than young adults to disclose their HIV status due to having steady sexual relationships and sense of responsibility [16,17]. Individuals who had never married had lower sensitivity (75.6%: 60.5–87.1) and PPV (85.0%: 70.2–94.3) compared with those who were currently (PPV 98.3%) or previously married (98.4%). However, the association between accurately self-reporting an HIV-positive status and marital status was lost when marital status was adjusted for age and other factors (Table 3).

Similar to other studies [4] sensitivity and PPV decreased with increasing time interval between HIV testing and self-reported HIV status (Fig. 2). It might be expected that individuals recently tested would live in denial (lower PPV), and gain acceptance over time (higher PPV), but this was not supported by the data, and we were not necessarily looking at time since first HIV-positive test. It is possible that individuals with longer time intervals were more likely not to believe the test results especially if they remained healthy, leading to misreporting their status. Being on ART has been shown to be associated with high sensitivity for self-reported HIV status [4]. We found no evidence for an association between current ART use and accurately reporting HIV-positive status, partly due to the substantial amount of missing data (30%) on ART use. Accuracy in self-reporting remained consistent for most individuals when we compared the first and last set of HIV test result and subsequent self-reported HIV status. However, there was evidence, albeit based on small numbers, that individuals who seroconverted between tests were more likely to misreport their HIV-positive status perhaps because they were still living in denial.

Accuracy of self-reported HIV status also depends on the context and setting in which information is being reported and perceived benefit or harm of disclosure. Our estimates of sensitivity and PPV were higher (92.1, 99.1%, respectively) in clinic settings compared with community settings (84.1, 97.7%) (Table 2). As patients, they may feel obligated to tell the truth for healthcare providers to take necessary precaution or in anticipation of optimized care. Unlike in community settings in which privacy issues (presence of family/friends nearby) and mistrust of fieldworkers/interviewers are likely to influence misreporting.

Sensitivity for self-reported HIV status increased from 83% during 2007–2010 to 91% (2011–2012) before dropping to 85% (2013–2018) (Table 2). The 2007–2010 period was the time annual HIV serosurveys were being introduced. By 2011, a total of four such surveys had been completed. Therefore, people were more likely to have had multiple tests during the 2011–2012 period. Also they were likely to feel more comfortable talking to study fieldworkers and therefore, more willing to share their HIV status than in the earlier period. As such, the observed higher sensitivity during 2011–2012 than in 2007–2010 are expected. The 2013–2018 period saw major changes in national HIV/ART guidelines including expansion of Option B+ [18,19] to all antenatal care clinics in Malawi in 2013 [20,21], and adoption of the 2015 WHO guidelines [22] on universal 'test and treat' in 2016 [23–25]. It might be expected that more people would be aware of their HIV status during this period resulting in higher sensitivity for HIV status. However, sensitivity was lower in 2013–2018 than in 2011–2012, probably because HIV serosurveys were no longer conducted in the HDSS during this period.

Our estimates of sensitivity are higher than those in prior studies from South Africa, Malawi and Kenya, which ranged from 26% in Malawi to 51.2% in South Africa [4,5]. This may be because our analysis was restricted to individuals who had been informed of their HIV results, in a population that had been frequently tested. While in prior studies, self-reporting preceded the HIV test; sensitivity estimates were based on responses to the question 'have you ever tested positive for HIV?' thereby including individuals who did not know their HIV status. However, in one of the studies, sensitivity and PPV

remained essentially the same in a subset of participants that reported knowing their status [4].

Our study is large and based on population-based data spanning over 10 years. We explored predictors of accurate self-reporting of HIV-positive status in SSA, including assessing its performance in different settings (clinic vs. community). A limitation to this study is that the findings may not be easily generalizable to other settings. The regular HIV serosurveys and other research studies conducted in the HDSS mean that participants are exposed to frequent HIV testing and are aware of their HIV status more than other settings. This may be the reason for the observed higher predictive values (even in community settings) compared with prior studies in the region. However, more people in SSA are now aware of their HIV status. In 2018, an estimated 85% (75–95) of PLWH in East and Southern Africa knew their status, higher than the estimated global 79% [26]. For 90% in the UNAIDS 90–90–90 [27] to be achieved, frequent HIV testing and retesting is required. This will help improve sensitivity of self-reported HIV – an important resource for HIV management programs and epidemiological studies.

In conclusion, the validity of self-reported HIV status was high. We observed very high specificity and NPV. Our estimates of sensitivity and PPV were higher than those reported in other studies in SSA. Being younger, interviewed in community settings and having longer duration since most recent HIV test was associated with less accurate reporting of HIV-positive status. Our findings confirm self-reported HIV status, and especially self-reported positive status, as a useful measure of HIV status when test data are unavailable.

Acknowledgements

J.R.G. conceived the study and contributed to design of the original data collection. A.D. contributed to data collection. J.R.G, S.C. and E.M. designed the analysis. S.C. led the statistical analysis, with contributions from J.R.G., I.D.S.S, E.M., and V.M. The article was written by S.C., with contributions from all other authors. All authors have read and approved the submitted version of the article.

Conflicts of interest

All studies contributing the data for current analysis were funded by the Wellcome Trust (Grant ref # 098610/Z/12/Z). S.C. is a Commonwealth scholar funded by the UK government.

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

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4.3 Summary

- This chapter assesses the validity of, and factors associated, with accurate self-reporting of HIV status in a population tested for HIV, using population-based data from Karonga HDSS. Self-reported HIV status was compared with biomarker-confirmed HIV test result among participants with information on HIV test results linked with a subsequent self-reported HIV status.
- There was high sensitivity and high specificity for self-reported HIV status (i.e., 86.4% (95% CI: 84.8-88.0) and 99.8% (99.7-99.9) respectively) with only 1.5% false negatives and 0.2% false positives. Both sensitivity and positive predictive values increased with age but decreased for individuals who had never married, and longer duration between HIV testing and self-reported HIV interview.
- There was evidence for an association between accurate self-report and setting in which it was obtained. HIV-infected individuals interviewed in clinic settings were more likely to accurately report their HIV-positive status than those in community settings (adjusted prevalence ratio: 1.07; 95% CI: 1.02-1.11).
- A key limitation with the data source is that Karonga HDSS maintains regular sero-surveys and other research studies in which HIV testing is done. Thus, this is a unique population where more people are aware of their HIV status. It is not surprising that accuracy of self-reports was very high. Hence, the results may not be easily generalisable to other settings. However, UNAIDS estimates indicate that 86% of HIV-infected individuals were aware of their HIV status in 2022. And the fact that the HIV prevalence estimates, and HIV-patient profile (demographic and socio-economic) are similar to some of ABC-DO settings (e.g., Zambia and Uganda) may mean that these findings can to some extent be extrapolated to ABC-DO settings.
- The finding that HIV-infected individuals are more likely to accurately self-report their HIV-positive status in clinical settings is also reassuring. ABC-DO study being a prospective hospital-based study, which was not HIV-focused, there was no incentive for women to lie about their HIV status. Besides, self-reported HIV status was obtained at two different time points (at recruitment and first symptoms questionnaire) enabling assessment of within-woman agreement.

Chapter 5 Pathways to breast cancer diagnosis for HIV-infected versus HIV-uninfected women

5.1 Introduction

The high mortality rates of breast cancer in SSA have been attributed, to a large extent, to advanced stage at presentation and/or diagnosis coupled with poor uptake and compliance with appropriate treatment[1-3]. Indeed in SSA, most breast cancer patients are diagnosed with advanced-stage disease[4] compared to high income countries (HICs) where breast cancer is usually diagnosed at early stages, when it is potentially curable. Among other reasons for advanced-stage breast cancers in SSA, delays in seeking care and getting a definitive diagnosis are likely major contributors[5]. Studies have shown that a delay in time period from when a woman first recognises breast cancer symptoms to first seeking care at a healthcare facility and to its diagnosis are associated with advanced stage at diagnosis and poorer survival[2,5,6].

Over the past decade, accessibility to HIV care and treatment for people with HIV in SSA has increased remarkably. As such, women with HIV now have improved access to clinical care and maintained contacts with healthcare service providers through antiretroviral therapy (ART) delivery services. Through these regular contacts with healthcare systems, it would be expected that HIV-infected women with symptoms suspicious of a breast cancer would present earlier than would HIV-uninfected women. However, few studies have examined the role of HIV status on the breast cancer diagnostic journey, and those who did had limited data on potential correlates of diagnostic interval from symptom recognition by the woman to definitive diagnosis. This chapter will take advantage of the wealth of data collected in the ABC-DO study to examine the length of the breast cancer pre-diagnostic journey, overall and by country, and whether it differs between HIV-infected and HIV-uninfected women in SSA.

5.2 Methods

5.2.1 Study participants and data collection

Study participants were women aged 18 years or older, recruited into the ABC-DO study, details of which have been outlined in Chapter 3. Briefly, at enrolment, women completed a face-to-face baseline interview which captured detailed clinical and epidemiological data such as age; ethnicity (categorised as black vs. non-black); formal education attained; usual place of residence (rural *vs* urban); access to nine household amenities used to generate site-specific tertiles of socio-economic position (SEP: low, medium and high)[7]; having any

other non-HIV chronic comorbidities (yes *vs* no) which included any of high blood pressure, heart disease, diabetes, history of cancer, anaemia, chronic obstructive pulmonary diseases, asthma, hepatitis, tuberculosis and any other chronic diseases. Body mass index (BMI, Kg/m^2) was derived from height and weight measured at recruitment. Data on HIV status was also collected. In South Africa, women who reported not being HIV-positive were tested for HIV whereas HIV status was self-reported in the rest of ABC-DO study sites.

Detailed woman-self-reported information was obtained on the pre-diagnostic experience including date women first noticed breast cancer symptoms and of subsequent contacts with formal and informal (e.g., traditional healers) healthcare providers. Breast cancer awareness before the cancer diagnosis was assessed at recruitment using indicators such as whether the woman had ever heard of breast cancer (yes *vs* no.do not know), knowledge of whether breast cancer is potentially curable if treated early (yes *vs* no/do not know). A separate breast cancer knowledge score ranging from 0 to 5 (highest score) was generated using the sum of positive answers (+1 each) to: (i) ever knowing anyone with breast cancer; (ii) believing breast cancer can be inherited; and negative answers (+1) to: believing breast cancer could be (iii) caught from others; caused by (iv) injury to the breast or (v) a curse or spiritual attack[7].

The data on breast cancer awareness and time to presentation and diagnosis were collected in all ABC-DO study sites except in South Africa where a slightly different questionnaire was used. Further, due to low HIV prevalence, women from Nigeria and in non-black groups in Namibia were excluded from the present analyses. Therefore, the results presented in this chapter are for black women from Namibia, Uganda, and Zambia only.

5.2.2 Breast cancer diagnostic interval definitions

Published studies on time to breast cancer diagnosis in HICs have defined time to breast cancer diagnosis in terms of delay to diagnosis, comprising of two parts; patient- and system or provider delays[8]. Patient delay is delay in seeking medical attention following the woman's self-discovery of potential breast cancer symptoms or failure to keep appointments. System or provider delay is delay between first contact with a healthcare provider and getting a definitive diagnosis. Foerster et al. have argued that these terms may not be directly applicable to SSA settings due to a likely complex interplay between patient- and health systems-related factors[5]. They proposed splitting the total pre-diagnostic interval into "pre-contact" and "post-contact" intervals i.e., A and B in Figure 5.1 below, respectively.

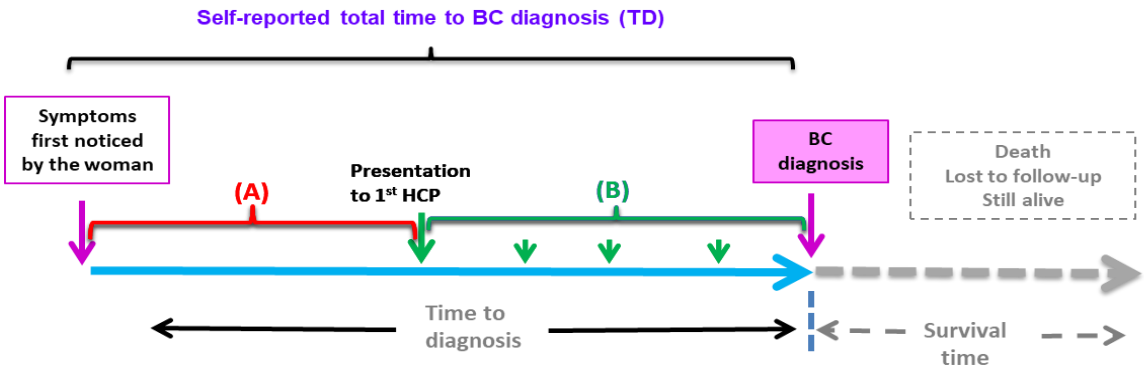

Figure 5.1 Illustration of time intervals to breast cancer diagnosis as captured in ABC-DO study (A: pre-contact interval; B: post-contact interval; TD: total pre-diagnostic interval)

The total pre-diagnostic interval (TD) is defined as the total time (in months) from the date when a woman first noticed her breast cancer symptoms to the date of definitive diagnosis. Pre-contact interval is the time interval from the date when a woman first noticed her breast cancer symptoms to the date when she first presented to a healthcare provider (formal or informal). Post-contact interval is the time interval from the date of first visit to a healthcare provider to the date of definitive diagnosis.

5.2.3 Data analysis

The primary outcome was length (in months) of the pre-diagnostic journey calculated from the date of symptom discovery to the date of definitive diagnosis of breast cancer. The latter was defined according to the European Network of Cancer Registries guidelines[9], which prioritise the date of biopsy or cytology over the date of hospital admission or date of diagnosis based on clinical examinations. The total pre-diagnostic interval was split into pre- and post-contact intervals as defined above. These intervals were reported as median and interquartile range (IQR) overall, and separately for women with and without HIV. Kaplan Meier curves were used to estimate the cumulative probability of being diagnosed since symptom discovery and since first visit to a healthcare provider. The lengths of each interval were compared between HIV-infected and HIV-uninfected women using negative binomial regression models. The crude model included HIV status as the main exposure yielding incidence rate ratio (IRR) comparing length of each interval between HIV-infected and HIV-uninfected women. Associations between each time interval and each of the available patient factors (socio-demographic and breast cancer awareness) were examined to determine factors associated with the outcome. Pearson's Chi-squared test was used to test the association between HIV status and each of the risk factors outlined above. Factors associated with both the outcome (time interval) and the exposure (HIV status), and not on

causal pathway, were considered potential confounders of the association between HIV status and each of the pre-diagnostic intervals. Each of the potential confounders was assessed and added sequentially to a minimally adjusted model with HIV status, age at breast cancer diagnosis and study population (i.e., country).

5.3 Results

Between September 2014 and December 2017, ABC-DO study recruited 1541 women with incident breast cancer in Nigeria (n= 402), Namibia (n= 502, including 104 non-black women), Uganda (n= 431) and Zambia (n= 206). Of these, 169 (11.0%) were HIV-infected, 1176 (76.3%) were HIV-uninfected and 196 (12.7%) had unknown HIV status. HIV prevalence was low among non-black women in Namibia (3 (2.9%) *vs* 98 HIV-uninfected women) and among all women in Nigeria (14 (3%) vs. 313). As such these patient subgroups (506) were excluded from the present analyses, leaving a total of 1035 black women from Namibia (n= 398), Uganda (n= 431) and Zambia (n=206).

5.3.1 Baseline characteristics of study participants

Among the 1035 women included in the analysis, 152 (15%) were HIV-infected, 765 (74%) were HIV-uninfected and 118 (11%) did not know their HIV status. HIV prevalence ranged from 13% in Uganda, and 14% in Namibia, to 18% in Zambia. Table 5.1 outlines socio-demographic and clinical characteristics at baseline (i.e., recruitment), by HIV status and study site.

Only age at breast cancer diagnosis, marital status, and presence of any non-HIV comorbidity were associated with HIV status. HIV-infected women were, relative to their HIV-uninfected counterparts, more likely to be younger at breast cancer diagnosis (mean = 46 years (SD: 10) vs. 51 (15) years) and unmarried (67% *vs* 55%, p= 0.007) (Table 5.1).

Overall, 604 (58%) of women presented with advanced stage breast cancer (i.e., TNM stage[10] III/IV). TNM stage was unknown for 75 (7%) of women. The percentage of women with advanced stage at diagnosis was high in both HIV-infected and HIV-uninfected women for all countries combined and for each country individually (Table 5.1).

Table 5.1 Baseline characteristics of the ABC-DO study participants, by HIV status and site

	Namibia (n=398)		Uganda (n=431)		Zambia (n=206)		All sites (n=1035)	
	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-
Characteristic	**N (%†)**	**N (%†)**	**N (%†)**	**N (%†)**	**N (%†)**	**N (%†)**	**N (%)**	**N (%†)**
Total (row % η)	**57 (14.3)**	**322 (80.9)**	**58 (13·5)**	**324 (75.1)**	**37 (18.0)**	**119 (57.8)**	**152 (14.6)**	**765 (73.9)**
Age at BC diagnosis mean (SD)	47 (10)	54 (16)	46 (9)	49 (13)	45 (10)	51 (15)	46 (10)	51 (15)
		P< 0.001		P= 0.25		P= 0.02		P< 0.0001
Education attained								
None/primary	26 (45.6)	173 (53.7)	33 (56.9)	189 (58.3)	15 (40.5)	65 (54.6)	74 (48.7)	427 (55.8)
Secondary/above	31 (54.4)	149 (46.3)	25 (43.1)	135 (41.7)	22 (59.5)	54 (45.4)	78 (51.3)	338 (44.2)
		P= 0.26		P= 0.84		P= 0.13		P= 0.11
Socio-economic position[β]								
Low	33 (57.9)	135 (41.9)	29 (50.0)	194 (59.9)	14 (37.8)	46 (38.7)	76 (50.0)	375 (49.0)
Medium	18 (31.6)	112 (34.8)	15 (25.9)	70 (21.6)	13 (35.1)	39 (32.8)	46 (30.3)	221 (28.9)
High	6 (10.5)	75 (23.3)	14 (24.1)	60 (18.5)	10 (27.0)	34 (28.5)	30 (19.7)	169 (22.1)
		P= 0.04		P= 0.36		P= 0.96		P=0.81
Married								
Yes	15 (26.3)	106 (32.9)	17 (29.3)	165 (50.9)	18 (48.7)	72 (60.5)	50 (32.9)	343 (44.8)
No	42 (73.7)	216 (67.1)	41 (70.7)	159 (49.1)	19 (51.3)	47 (39.5)	102 (67.1)	422 (55.2)
		P= 0.32		P= 0.002		P=0.20		P= 0.007
Ever heard about breast cancer[ζ]								
Yes	49 (85.9)	274 (85.1)	42 (72.4)	257 (79.3)	34 (91.9)	106 (89.1)	125 (82.2)	637 (83.3)
No/not sure	8 (14.1)	48 (14.9)	16 (27.6)	67 (20.7)	3 (8.1)	13 (10.9)	27 (17.8)	128 (16.7)
		P= 0.86		P=0.24		P= 0.62		P= 0.76
Thinks BC is curable[ζ]								
Yes	39 (68.4)	249 (77.3)	24 (41.4	128 (39.5)	21 (56.8)	83 (69.8)	84 (55.3)	460 (60.1)
No/not sure	18 (31.6)	73 (22.7)	34 (58.6	196 (60.5)	16 (43.2)	36 (30.2)	68 (44.7)	305 (39.9)
		P= 0.15		P= 0.79		P= 0.14		P= 0.26
BC knowledge score								
Low	33 (57.9)	169 (52.5)	34 (58.6)	168 (51.9)	25 (67.6)	86 (72.3)	92 (60.5)	423 (55.3)
Medium	16 (28.1)	116 (36.0)	21 (36.2)	137 (42.3)	12 (32.4)	29 (24.4)	49 (32.2)	282 (36.9)
High	8 (14.0)	37 (11.5)	3 (15.2)	19 (5.8)	0 (0)	4 (3.3)	11 (7.3)	60 (7.8)
		P= 0.49		P= 0.64		P= 0.36		P= 0.49
Area of residence [ζ]								
Urban	32 (56.1)	180 (55.9)	15 (25.9)	89 (27.5)	26 (70.3)	73 (61.3)	73 (48.0)	342 (44.7)
Rural	25 (43.9)	142 (44.1)	43 (74.1)	235 (72.5)	11 (29.7)	46 (38.7)	79 (52.0)	423 (55.3)
		P= 0.97		P= 0.80		P=0.33		P= 0.45
Any comorbidities[α]								
No	35 (61.4)	150 (46.6)	48 (82.8)	222 (68.5)	30 (81.1)	74 (62.2)	113 (74.3)	446 (58.3)
Yes	22 (38.6)	172 (53.4)	10 (17.2)	102 (31.5)	7 (18.9)	45 (37.8)	39 (25.7)	319 (41.7)
		P= 0.04		P= 0.03		P=0.03		P< 0.001
Stage at BC diagnosis								
I/II	21 (36.8)	117 (36.3)	14 (24.0)	105 (32.4)	10 (27.0)	43 (36.1)	45 (29.6)	265 (34.6)
III/IV	36 (63.2)	205 (63.7)	36 (62.1)	201 (62.0)	19 (51.4)	54 (45.4)	91 (59.9)	460 (60.1)
Unknown	0 (0)	0 (0)	8 (13.9)	18 (5.6)	8 (21.6)	22 (18.5)	16 (10.5)	40 (5.3)
		P= 0.94		P= 0.38		P= 0.35		P= 0.44

NK= not known. BC= breast cancer

η row percentage by HIV status including small number of women whose HIV status was unknown; 19 in Namibia, 49 in Uganda and 50 in Zambia

† Column percentage including missing values where applicable

‡ All P-values in this table are chi-squared test P-values comparing HIV+ and HIV- women only, except for age at breast cancer diagnosis where Student's T-test was used

β Socio-economic position (SEP) was derived from a score of combined self-reported access to amenities including home ownership, indoor water, flush toilet, electricity, vehicle, refrigerator, landline, gas or electric stove and a bed. SEP categories (low, middle or high) were constructed based on country specific distribution of the SEP score tertiles.

α Comorbidities include: Tuberculosis, Hepatitis, Hypertension, Heart disease, Diabetes, Anaemia, COPD, Asthma, other cancer, other infections and other diseases

5.3.2 Length of the pre-diagnostic interval

Of the 1035 women included in this study, a further group of women (n=65) were excluded either because their first reported symptom was over 5 years ago (n=50, likely to be a previous condition) or the date of first symptom discovery was later than the date of diagnosis. In post-contact interval analyses, 42 women were also excluded because the date of diagnosis preceded the self-reported date of the first visit to a healthcare provider.

Overall, the median length (in months) of the total pre-diagnostic interval was 8.4 months (IQR 3.8, 19.3). The interval ranged from 6.5 (2.4, 15.2) months in Namibia to 8 (2.9, 16.4) months in Zambia and 11 (5.6, 207) months in Uganda.

5.3.3 Length of pre-diagnostic intervals and HIV status

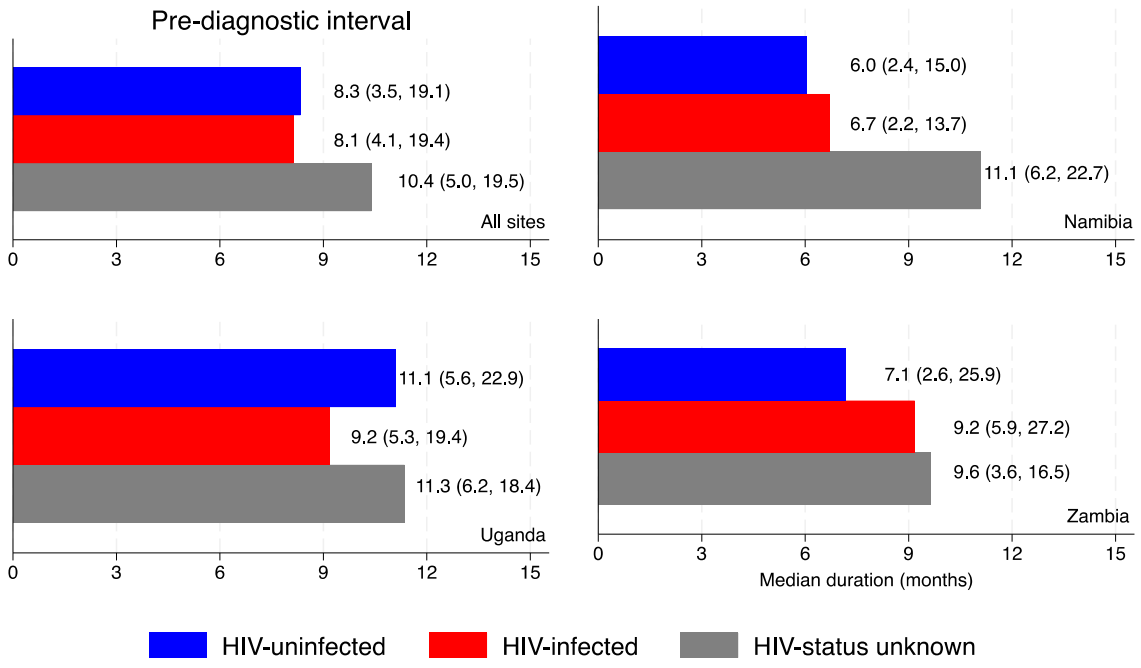

Figure 5.2 Median (IQR) length (in months) of pre-diagnostic intervals from symptom recognition to diagnosis of breast cancer in ABC-DO women overall, and by HIV status and country

The length of the total pre-diagnostic interval was similar between HIV-infected and HIV-uninfected women for all sites combined (Figure 5.2). However, the difference in interval by HIV status varied across sites. In Namibia, HIV-infected and HIV-uninfected women had roughly similar lengths of pre-diagnostic interval. In Uganda HIV-infected women had slightly shorter interval (9.2 months; 5.3,19.4) than did HIV-uninfected women (11.1 months; 5.6,

22.9). Whilst in Zambia, HIV-infected women had slightly longer pre-diagnostic interval (9.2 months; 5.9, 27.2) compared with their HIV-uninfected counterparts (7.1 months; 2.6, 25.9) (Figure 5.2).

The Kaplan Meier curves (Figure 5.3) did not show any differences in proportion diagnosed by time since first symptom between HIV-infected and HIV-uninfected women except for Zambia (e.g., a higher proportion of HIV-uninfected women (28%) was diagnosed within three months of symptom recognition compared to HIV-infected women (19%)).

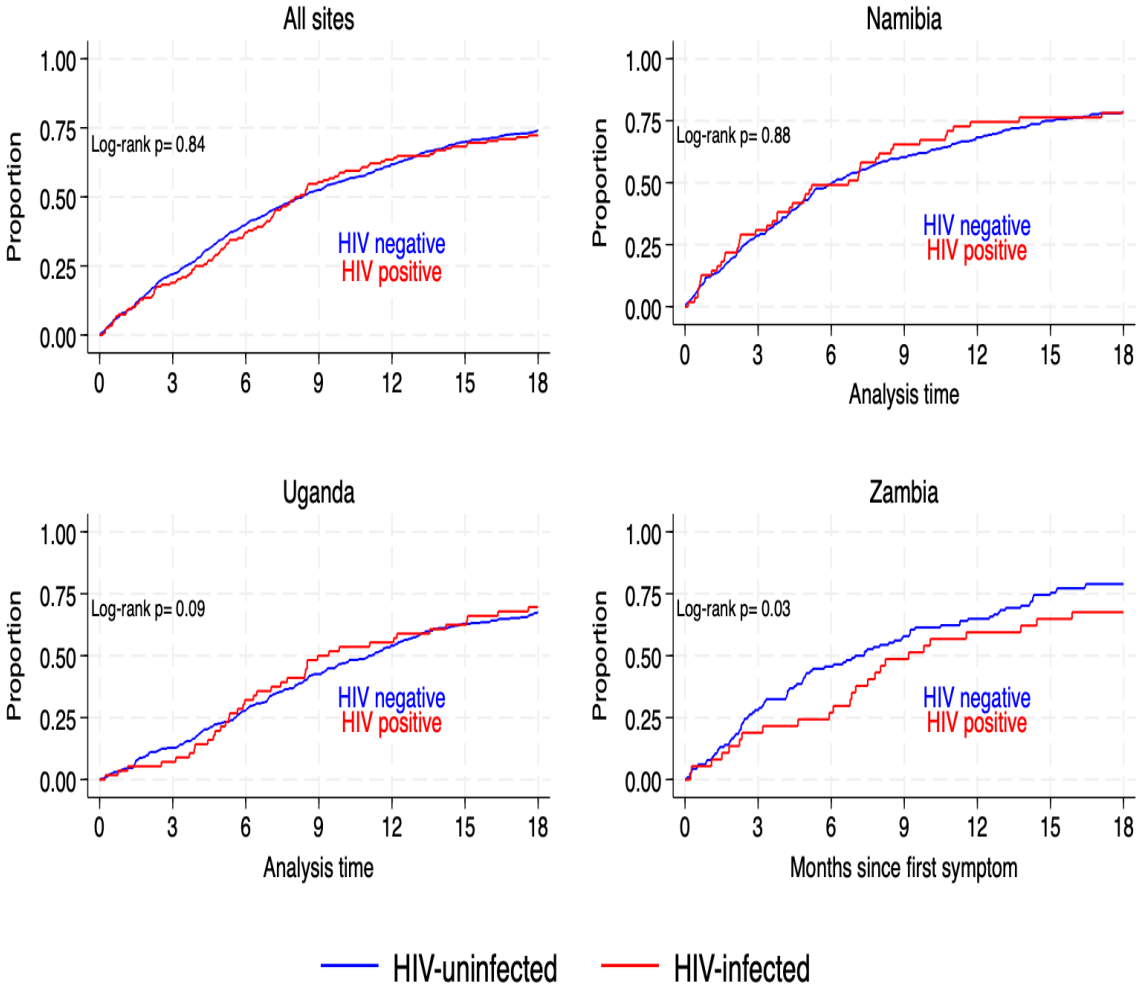

Figure 5.3 Cumulative probability of being diagnosed with breast cancer by time since first symptom recognition according to HIV status and country.

Table 5.2 shows crude and adjusted IRRs for the association between length of pre-diagnostic interval and HIV status. There was no evidence for an association between pre-

diagnostic interval and HIV status even after adjusting for relevant patient and breast cancer awareness factors (adjusted IRR 1.06; 0.89-1.28). Relative to Namibian women, the length of the pre-diagnostic interval was 38% longer among women in Uganda (adjusted IRR 1.38; 1.17-1.63). Women who were uneducated (none/primary education) were associated with 40% increase in their length of pre-diagnostic journey than women who had secondary or higher education (adjusted IRR 1.40; 1.19-1.65). There was borderline evidence suggesting a longer pre-diagnostic interval for women in Zambia (vs Nambian women: adjusted IRR 1.23; 0.99 – 1.54); for unmarried women (vs. married women: adjusted IRR 1.14; 0.99 – 1.31); and women with a low socio-economic position (SEP) (vs. medium/high SEP: adjusted IRR 1.14; 0.97 – 1.33) (Table 5.2).

Table 5.2 Crude and adjusted IRRs for association between length of pre-diagnostic interval, pre- and post-contact intervals and HIV status adjusted for relevant patient factors in ABC-DO HIV study

	All sites[α]					
	Pre-contact interval		Post-contact interval		Total pre-diagnostic interval	
	Crude IRR (95% CI)	Adjusted IRR (95% CI)	Crude IRR (95% CI)	Adjusted IRR (95% CI)	Crude IRR (95% CI)	Adjusted IRR (95% CI)
Variable						
HIV positive (vs negative)	1.16 (0.89-1.50)	1.18 (0.89-1.55)	0.88 (0.69-1.11)	0.92 (0.72-1.18)	1.01 (0.85-1.20)	1.06 (0.89-1.28)
Study population group						
Namibia	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Uganda	1.23 (1.01-1.51)	1.24 (0.98-1.59)	1.48 (1.23-1.78)	1.72 (1.38-2.14)	1.31 (1.14-1.50)	1.38 (1.17-1.63)
Zambia	1.2 (0.94-1.54)	1.4 (1.00-1.96)	1.06 (0.84-1.33)	1.06 (0.79-1.42)	1.09 (0.92-1.29)	1.23 (0.99-1.54)
Age group						
18-39	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
40-49	1.01 (0.79-1.29)	1.01 (0.77-1.34)	1.19 (0.95-1.49)	1.09 (0.85-1.39)	1.06 (0.89-1.25)	0.99 (0.82-1.19)
50-59	1.21 (0.94-1.57)	1.13 (0.84-1.54)	1.18 (0.93-1.50)	1.04 (0.80-1.37)	1.13 (0.94-1.34)	1.04 (0.85-1.28)
60+	1.51 (1.17-1.95)	1.25 (0.89-1.75)	1.15 (0.90-1.450	0.91 (0.67-1.23)	1.22 (1.03-1.46)	1.00 (0.80-1.27)
Primary/no education (vs secondary/higher)	1.44 (1.20-1.72)	1.32 (1.04-1.68)	1.42 (1.21-1.68)	1.49 (1.20-1.85)	1.4 (1.24-1.58)	1.4 (1.19-1.65)
Low SEP[α] (vs medium/high)	1.18 (0.99-1.41)	1.03 (0.82-1.30)	1.24 (1.05-1.46)	1.21 (0.98-1.49)	1.24 (1.10-1.40)	1.14 (0.97-1.33)
Not employed (vs employed)	1.15 (0.93-1.42)	0.89 (0.68-1.17)	1.00 (0.83-1.21)	0.96 (0.76-1.22)	1.04 (0.90-1.19)	0.91 (0.76-1.09)
Not married (vs married)	1.17 (0.97-1.40)	1.18 (0.96-1.45)	1.07 (0.91-1.27)	1.22 (1.00-1.47)	1.11 (0.98-1.25)	1.14 (0.99-1.31)
Rural (vs urban residence)	1.24 (1.04-1.49)	1.14 (0.91-1.43)	1.08 (0.92-1.28)	0.77 (0.62-0.96)	1.16 (1.02-1.31)	0.93 (0.80-1.09)
Any comorbidity[†] (vs none)	0.89 (0.74-1.06)	0.86 (0.69-1.06)	0.98 (0.83-1.16)	1.07 (0.88-1.30)	0.92 (0.81-1.04)	0.96 (0.83-1.11)
Ever heard about BC (yes vs no/not sure)	0.76 (0.60-0.97)	0.9 (0.69-1.18)	1.13 (0.90-1.40)	1.34 (1.05-1.72)	0.97 (0.83-1.15)	1.10 (0.92-1.32)
Knowledge BC is curable (yes vs no/not sure)	0.82 (0.68-0.98)	0.94 (0.75-1.18)	0.87 (0.74-1.03)	1.11 (0.91-1.36)	0.83 (0.73-0.94)	0.99 (0.85-1.15)

BC = breast cancer

α: Excluding South Africa due to different questionnaire being use, and non-black women in Namibia due to small number of women with HIV

: Socio-economic position (SEP) was derived from a score of combined self-reported access to amenities including home ownership, indoor water, flush toilet, electricity, vehicle, refrigerator, landline, gas or electric stove and a bed. SEP categories (low, middle or high) were constructed based on country specific distribution of the SEP score tertiles.

†: Comorbidities include: Tuberculosis, Hepatitis, Hypertension, Heart disease, Diabetes, Anaemia, COPD, Asthma, other cancer, other chronic infections and other chronic diseases

Similarly, there was no evidence for differences in length of the pre- and post-contact interval between HIV-infected and HIV-uninfected women. Only education and being from Uganda were associated with the lengths of the pre- and post-contact interval. However, the associations were stronger for the post-contact interval than for pre-contact interval, suggesting that any observed increases in length of total pre-diagnostic interval were largely driven by longer post-contact intervals (Table 5.2).

5.4 Discussion

This chapter focused on the pre-diagnostic interval (i.e., time to breast cancer diagnosis) for women diagnosed with breast cancer in SSA and examined whether the length of the interval differs between HIV-infected and HIV-uninfected women. Overall, the length of pre-diagnostic interval among ABC-DO women was much longer than what is reported in developed countries[8,11-15], but consistent with previous reports in other SSA settings[16-18]. This is expected in settings such as SSA where population-based screening is non-existent[19,20] and breast cancer awareness is low[7,21]. HIV-infected women were as likely to have longer diagnostic intervals as did HIV-uninfected women i.e., there was no evidence for an association between length of pre-diagnostic interval and HIV status. It is therefore not surprising that most ABC-DO women presented with advanced-stage breast cancer regardless of HIV status across all study sites, consistent with previous reports of late stage at diagnosis of breast cancer in SSA[4,22,23]. A number of studies in SSA also found no differences in tumour stage at diagnosis between HIV-infected and uninfected women[19,24-26].

Only being of low SEP, uneducated, and being from Uganda or Zambia was independently associated with longer lengths of pre-diagnostic intervals. Further, the length of pre-diagnostic interval appeared to largely be driven by longer post-contact intervals from first visit to a healthcare provider to definitive diagnosis. These findings highlight the importance of promoting breast cancer awareness among both women and healthcare providers, and the need for efficient patient navigation and referral systems. They also expose a missed opportunity for early detection of breast cancer especially among women with HIV who are already in regular contact with the healthcare system for HIV services.

Strengths of this study included its large size, substantial numbers of women with HIV, the detailed data on pre-diagnostic journey and the multi-country design, enabling comparison across different SSA settings. However, there are some limitations. Firstly, the hospital-based nature of the study design might limit generalizability of observed results because not all women with breast cancer end up at the participating hospitals. Secondly, women in ABC-DO self-reported their lengths of pre-diagnostic intervals. Thus, the findings are likely to have

been affected by random (non-differential) measurement error as women would not have been able to precisely remember the dates of symptom recognition and all related contacts. Such errors would have diluted the association between HIV status and interval lengths. The findings might also have been affected by differential measurement errors if the level of recollection differed by HIV status and, if so, recall bias would have occurred but it would be difficult to say what its direction would be. However, the fact that both HIV-infected and HIV-uninfected women had longer pre-diagnostic intervals and subsequent advanced breast cancer stage at diagnosis is reassuring as it is consistent with previous studies in SSA, which have shown no differences in tumour characteristics (e.g., stage, grade and receptor status) at diagnosis between HIV-infected and uninfected women[24-27]. The reported prevalence of advanced-stage at diagnosis were high regardless of HIV status in the ABC-DO study, one of largest cohorts with HIV-infected breast cancer women in SSA (65% HIV+. Vs. 60% HIV- women, adjusted Odds ratio (AOR) 1.03, 95% CI: 0.63 – 1.67))[22]

In conclusion, ABC-DO women experienced longer pre-diagnostic journeys from symptom recognition to first contact with a healthcare provider to definitive breast cancer diagnosis. Overall, the length of pre-diagnostic intervals did not differ between HIV-infected and HIV-uninfected women. More consideration should be given to promoting breast cancer awareness among both the women and their healthcare providers. Among HIV-infected women, deliberate efforts should made to assess the feasibility and effectiveness of integrating breast cancer care into the already functional HIV and cervical cancer services in SSA including screening for breast cancer and implementation of efficient patient navigation systems for early breast cancer diagnosis and treatment.

5.5 Summary

- This chapter examined the time to breast cancer diagnosis from symptom recognition to a definitive breast cancer diagnosis, and whether this time interval differs between HIV-infected and uninfected women using data from the ABC-DO study.
- Among 1035 ABC-DO women (152 (15%) HIV-infected, 765 (74%) HIV-uninfected), the median length of the pre-diagnostic interval was 8.4 months (IQR 3.8, 19.3) overall; 8.1 (4.1, 19.4) in HIV-infected *vs* 8.3 (3.5, 19.1) in HIV-uninfected women.
- There was no association between length of pre-diagnostic interval and HIV status even after adjusting for relevant patient and breast cancer awareness factors (adjusted IRR 1.06; 95% CI: 0.89-1.28).
- Ultimately most women presented with advanced-stage breast cancer regardless of their HIV status consistent findings from previous studies in the region.

- More efforts should focus on promoting breast cancer awareness in both groups of women and healthcare providers including assessing the feasibility and effectiveness of integrating breast cancer care (e.g., breast cancer screening) into the already existing HIV and cervical cancer services in most countries in SSA.

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Chapter 6 Overall survival disparities between women and without HIV

6.1 Introduction

This chapter addresses research aim 3 which is to examine differences in overall survival after a breast cancer diagnosis by HIV status, including reasons for such differences. I used data from the ABC-DO study, details of which have been described in chapter 3. As shown in chapter 2, the literature review, most studies consistently reported that HIV-infected women with breast cancer are associated with poorer overall survival compared with HIV-uninfected women with breast cancer. However, most of the early studies) i.e., published studies at the beginning of the PhD) were smaller in size and had shorter lengths of follow-up, leading to statistically non-significant results.

Therefore, in this chapter, I used data from the ABC-DO study, one of the largest breast cancer cohorts in sub-Saharan Africa (SSA), to estimate overall survival following a breast cancer diagnosis in HIV-infected women relative to their HIV-uninfected counterparts with breast cancer. The hypothesis was that HIV-infected women diagnosed with breast cancer have significantly increased risk of all-cause mortality compared with HIV-uninfected women with breast cancer. As part of investigating the determinants of these survival disparities, I also investigated associations between patient and tumour characteristics (e.g., tumour grade and stage at diagnosis, and tumour receptor status) for which evidence for differences by HIV status in SSA was inconclusive in earlier studies – either due to lack of data or small sample size, both of which are overcome in the ABC-DO study.

The results of these analyses are presented as a research paper 2 which was published in The Lancet HIV on 31 March 2022

6.2 Research paper 2

Disparities in breast cancer survival between women with and without HIV across sub-Saharan Africa (ABC-DO): a prospective, cohort study

(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9031563/pdf/nihms-1793903.pdf)

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Please note that a cover sheet must be completed <u>for each</u> research paper included within a thesis.

SECTION A – Student Details

Student ID Number	LSH396778	**Title**	Mr.
First Name(s)	Steady Jerome Dickson		
Surname/Family Name	Chasimpha		
Thesis Title	Breast cancer in women living with HIV in Sub-Saharan Africa: presentation, diagnosis, and survival		
Primary Supervisor	Prof. Isabel dos-Santos-Silva		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

<u>SECTION B – Paper already published</u>

Where was the work published?	The Lancet HIV Journal		
When was the work published?	31 March 2022		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the first and corresponding author on this paper. I developed the analytical plan, and conducted all statistical analyses, and wrote the first draft of the manuscript with contributions from all co-authors.

SECTION E

Student Signature	[redacted]
Date	21 October 2023

Supervisor Signature	[redacted]
Date	21 October 2023

Disparities in breast cancer survival between women with and without HIV across sub-Saharan Africa (ABC-DO): a prospective, cohort study

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Lancet HIV 2022; 9: e160–71

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Summary

Background Studies have shown increased mortality among women living with HIV diagnosed with breast cancer compared with HIV-negative women with breast cancer. We aimed to examine how this HIV differential varies by patient or breast tumour characteristics.

Methods The African Breast Cancer–Disparities in Outcomes (ABC-DO) study is a prospective cohort of women (aged ≥18 years) with incident breast cancer recruited consecutively at diagnosis (2014–17) from hospitals in Namibia, Nigeria, South Africa, Uganda, and Zambia. Detailed clinical and epidemiological data, including self-reported or tested HIV status, were collected at baseline. Participants were actively followed up via telephone calls every 3 months. The primary outcome was all-cause mortality, assessed in all women who had at least one updated vital status after baseline interview. Using Cox regression, we examined differences in overall survival by HIV status in the cohort, and across country and patient subgroups, adjusted for age, tumour grade, and tumour stage at cancer diagnosis.

Findings Between Sept 8, 2014, and Dec 31, 2017, we recruited 2154 women with primary breast cancer, 519 of whom were excluded due to their countries having small numbers of women with HIV for comparison. Among the remaining 1635 women, 313 (19%) were living with HIV, 1184 (72%) were HIV negative, and 138 (9%) had unknown HIV status. At breast cancer diagnosis, women with HIV were younger and had lower body-mass index (BMI) than their HIV-negative counterparts, but had similar tumour stage, grade, and receptor subtypes. At the end of the follow-up (Jan 1, 2019), a higher proportion of women with HIV (137 [44%] of 313) had died than had HIV-negative women (432 [37%] of 1184). Crude 3-year survival was 9% lower for women with HIV (46% [95% CI 40–53]) than for HIV-negative women (55% [52–59]; hazard ratio (HR) 1·41 [1·15–1·74]). The HIV survival differential did not differ by age, BMI, tumour subtype, or tumour grade, but was stronger in women with non-metastatic disease (3-year survival 52% HIV-positive *vs* 63% HIV-negative women, adjusted HR 1·65 [1·30–2·10]), whereas women with metastatic cancer had low survival, regardless of HIV status.

Interpretation The larger survival deficit among women with HIV with non-metastatic breast cancer calls for a better understanding of the reasons underlying this differential (eg, biological mechanisms, health behaviours, detrimental HIV–breast cancer treatment interactions, or higher HIV background mortality) to inform strategies for reducing mortality among this patient group.

Funding Susan G Komen, International Agency for Research on Cancer, National Cancer Institute, and UK-Commonwealth Scholarships.

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Introduction

Breast cancer is the most common female cancer worldwide.[1] Although it is not an HIV-associated cancer, breast cancer is common in women living with HIV.[2] In 2012, an estimated 6325 new breast cancer cases were diagnosed among 16·0 million women with HIV globally.[2] The breast cancer burden in this population is expected to increase, partly due to improved survival outcomes in women with HIV as a result of the rollout of antiretroviral therapy (ART) for HIV,[3] meaning that women with HIV now live to ages when breast cancer incidence is highest.

Globally, most women with HIV reside in low-resource and high HIV-prevalence settings, such as sub-Saharan

Research in context

Evidence before this study

We identified a recent systematic review of studies published up to Jan 1, 2020, and updated it to Jan 1, 2021, by searching the Embase and PubMed (Ovid) databases using the search terms "breast cancer", "HIV", and "survival", with no language restrictions. The systematic review, comprising seven distinct study populations, showed that women living with HIV diagnosed with breast cancer had increased all-cause mortality compared with their HIV-negative counterparts with breast cancer, both in North America and sub-Saharan Africa. However, the review also highlighted marked between-study heterogeneity in the magnitude of the differences in mortality between women with and without HIV (increases of 1·6–4·6 times); studies with a small number of women with HIV; and, specifically in sub-Saharan Africa, studies with suboptimal follow-up owing to high losses to follow-up. Our updated search identified only one additional publication, from our African Breast Cancer–Disparities in Outcomes (ABC-DO) study, which showed a 1·5-times increase in all-cause mortality among women with HIV diagnosed with breast cancer in sub-Saharan Africa. None of these studies examined whether differences in overall survival vary by patient or tumour characteristics between women with and without HIV diagnosed with breast cancer.

Added value of this study

The ABC-DO study is a multi-country, hospital-based, prospective study that recruited women with incident breast cancer who were diagnosed in 2014–17 in five sub-Saharan Africa countries (Namibia, Nigeria, South Africa, Uganda, and Zambia) with varying HIV prevalence and different health-care systems. Detailed clinical and epidemiological data were collected at baseline, including self-reported or tested HIV status, and the cohort underwent active follow-up by mobile phone every 3 months. The ABC-DO study has the largest number of women with HIV diagnosed with breast cancer and lowest loss-to-follow-up ever reported in sub-Saharan Africa. We examined how the previously reported association between HIV status and survival after a diagnosis of breast cancer in the ABC-DO cohort might be modified by other factors. 3-year overall survival was lower for women with HIV than for HIV-negative women.

Implications of all the available evidence

The findings of the present study show that women with HIV diagnosed with breast cancer were at higher risk of dying within 3 years of their cancer diagnosis than their HIV-negative counterparts. Identifying the reasons for the higher all-cause mortality among women with HIV (eg, underlying biological mechanisms, poor access to [or compliance with] appropriate treatment regimens, detrimental HIV–breast cancer treatment interactions, or simply increased background mortality associated with HIV) is crucial if early deaths among this patient group are to be prevented.

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Africa. Breast cancer survival in sub-Saharan Africa is low (<50% at 5 years in most sub-Saharan Africa countries[4]) compared with 85–90% in high-income countries,[5] and is lower among women with HIV. Previous studies (appendix p 2) indicate increased all-cause mortality after breast cancer diagnosis among women with HIV compared with setting-matched HIV-negative women. This is not surprising as women with HIV have, in general, higher mortality rates than the general population.[6] In sub-Saharan Africa, estimates of the excess mortality seen among women with HIV (*vs* HIV-negative women) diagnosed with breast cancer ranged from an increase of 40–50% in South Africa and Mozambique to 80–100% in Botswana and Uganda.[7–10] Similarly, studies in the USA[11–15] showed an adjusted 50% and 80% increased risk for all-cause and breast cancer-specific mortality, respectively (appendix p 2). A meta-analysis reported a pooled-adjusted 90% increased risk,[16] albeit with marked between-study heterogeneity as most studies were either based on small numbers of women with HIV and, specifically in sub-Saharan Africa, had suboptimal follow-up time or losses to follow-up of greater than 40% (appendix p 2).[8,9]

The reasons for increased mortality in women with HIV compared with HIV-negative women with breast cancer remain unclear. This disparity might solely reflect the increased background mortality among women with HIV versus the general population. Alternatively, survival gaps might occur in women with HIV if their compromised immune system facilitates tumour progression, if they have poorer prognostic factors for breast cancer, if treatment regimens and intensities differ by HIV status, or if there are ART–chemotherapy interferences.[8,17,18] Women with HIV are diagnosed with breast cancer at younger ages than are HIV-negative women because women with HIV are typically younger than the general population. However, there is little or unclear evidence that stage at cancer diagnosis differs by HIV status. Most studies in the USA have shown that women with HIV are more likely to present with advanced-stage breast cancer, whilst most studies in sub-Saharan Africa have indicated either no such differences or only a modest excess in the prevalence of advanced-stage at diagnosis of breast cancer among women with HIV.[16] Excess weight is associated with poorer overall survival after a breast cancer diagnosis.[19] Being underweight or overweight also complicates HIV management and could contribute to increased cardiovascular disease risk or mortality (or both).[20] Finally, the survival deficits in women with HIV with breast cancer can vary by tumour hormone receptor status. ART affects breast tissue, with about 5% of men on ART experiencing breast enlargement (including

See Online for appendix

gynaecomastia[21]) suggesting a potential role of ART on circulating sex hormone concentrations. Therefore, the difference in survival after a breast cancer diagnosis between women with and without HIV (hereafter referred to as the HIV differential) might reflect, at least in part, an ART effect that could differ according to the tumour hormone receptor status. To date, no study has examined whether the HIV differential varies across patient subgroups defined by patient and tumour characteristics at diagnosis.

The African Breast Cancer–Disparities in Outcomes (ABC-DO) study is a multi-country prospective study of women newly diagnosed with breast cancer in five sub-Saharan Africa countries.[22] In a previous ABC-DO analysis,[23] women with HIV experienced a 48% (95% CI 22–81) increase in all-cause mortality after adjusting for age and tumour stage at diagnosis. In this analysis, we aimed to examine whether prognostic factors (such as age, stage, receptor status, and body-mass index [BMI]) explain the lower survival outcomes in women with HIV than in HIV-negative women and explore how the HIV differential varies across different sub-Saharan Africa settings and patient subgroups.

Methods

Study design and setting

The ABC-DO study recruited women with incident primary breast cancer in five countries in sub-Saharan Africa: Namibia, South Africa, and Zambia in southern Africa where HIV prevalence is high, Uganda in east Africa where HIV prevalence is intermediate, and Nigeria in west Africa where HIV prevalence is low.

Participants with a diagnosis of breast cancer were recruited from participating hospitals. The characteristics of participating hospitals and the study protocol have been described in detail previously.[22] The study was approved by all institutional ethics committees (appendix p 1). All participants provided informed written or thumbprint consent before recruitment.

Procedures

Between Sept 8, 2014, and Dec 31, 2017, women (aged ≥18 years) with cytological, histological (>80% of all participants[23]), or clinical diagnosis of primary breast cancer were recruited into the study. Participants answered a face-to-face baseline interview, and consented to study access to their medical records, to provide tumour tissue specimens, and to be actively followed up via telephone interviews every 3 months. The baseline questionnaire included detailed socio-demographic data, such as age, formal education attained, access to nine household amenities used to generate site-specific tertiles of socioeconomic position,[23,24] knowledge (before diagnosis) that breast cancer is curable if detected early, cohabitation status, residential status (urban *vs* rural), and presence of other non-HIV comorbidities. BMI was derived from height and weight measured at breast cancer diagnosis. HIV status was also captured at breast cancer diagnosis. In South Africa, all participants who did not report being HIV-positive were tested for HIV.[18] Those who refused were considered to be of unknown HIV status. For all other sites, HIV status was self-reported on the baseline questionnaire and also on the presenting symptoms questionnaire. For this analysis, a woman was considered HIV-positive if responses were positive on either questionnaire.

Data on current ART use, CD4 count, and HIV RNA (HIV-1 *vs* HIV-2) were also collected. Standard pro formas were used to extract clinical, pathological, and treatment information from hospital records on tumour TNM stage[25] (assessed clinically using ultrasound, x-ray, or surgical information); cytology or histology; grade; and oestrogen, progesterone, and human epidermal growth factor 2 (HER2) receptor status. Oestrogen-positivity and progesterone-positivity were defined as at least 1% immunohistochemistry staining for the respective receptor, and HER2-positivity as an immunohistochemistry score of 3 by immunohistochemistry or a positive fluorescence in-situ hybridisation result.

Follow-up was done actively via telephone calls every 3 months to the woman or her next-of-kin. At each contact, the date, vital status, and contact details were updated. The ABC-DO protocol was implemented using a specifically designed mHealth application that prompted real-time to-call lists, resulting in much lower loss to follow-up (5% at 3 years) and timely study notification of deaths (median 9·1 weeks [IQR 3·9–14·0]), most of which were reported by the next-of-kin (92%).[26]

Outcomes

The primary outcome was all-cause mortality, analysed for all women who had at least one updated vital status after baseline interview. We analysed overall survival up to 3 years by HIV status, on a time-since-diagnosis scale (ie, date of breast cancer diagnosis was time zero). Follow-up commenced on the latest date of either breast cancer diagnosis or—effectively incorporating left-censoring—ABC-DO recruitment date and continued until the earliest of: date of death from any cause, date last known alive (among those lost to follow-up), or administrative censoring on the earliest of 3 years post-diagnosis or Jan 1, 2019.

Statistical analysis

As per the published protocol,[22] the ABC-DO study invited all eligible women to participate over a period of at least 2 years in each country in order to recruit at least 300 women in each participating hospital. For an exposure prevalence of 30% and 50%, respectively, and over 3-year follow-up, ABC-DO would have 80% power to detect hazard ratios (HRs) of 1·7 and 2·6 for 100 deaths in smaller sites, and 1·5 and 2·1 for 160 deaths in larger sites, assuming 0·85 and 0·5 survival probabilities for stage I or II and stage III

	Namibia (n=384)		South Africa (n=632)		Uganda (n=421)		Zambia (n=198)		All sites (n=1635)	
	HIV positive, n (%)	HIV negative, n (%)	HIV positive, n (%)	HIV negative, n (%)	HIV positive, n (%)	HIV negative, n (%)	HIV positive, n (%)	HIV negative, n (%)	HIV positive, n (%)	HIV negative, n (%)
Total*	57 (14·8%)	309 (80·5%)	163 (25·8%)	446 (70·6%)	57 (13·5%)	315 (74·8%)	36 (18·2%)	114 (57·6%)	313 (19·1%)	1184 (72·4%)
Age at diagnosis, years										
18–29	1 (2%)	14 (4%)	3 (2%)	6 (1%)	4 (7%)	20 (6%)	3 (8%)	9 (8%)	11 (3%)	49 (4%)
30–39	14 (25%)	50 (16%)	30 (18%)	42 (9%)	7 (12%)	73 (23%)	10 (28%)	22 (19%)	61 (20%)	187 (16%)
40–49	23 (40%)	74 (24%)	73 (45%)	89 (20%)	27 (47%)	86 (27%)	13 (36%)	22 (19%)	136 (44%)	271 (23%)
50–59	13 (23%)	79 (26%)	34 (21%)	108 (24%)	13 (23%)	69 (22%)	10 (28%)	30 (26%)	70 (22%)	286 (24%)
60–69	5 (9%)	45 (15%)	18 (11%)	102 (23%)	6 (11%)	40 (13%)	0	14 (12%)	29 (9%)	201 (17%)
≥70	1 (2%)	47 (15%)	5 (3%)	99 (22%)	0	27 (9%)	0	17 (15%)	6 (2%)	190 (16%)
p value	..	p=0·008	..	p<0·0001	..	p=0·014	..	p=0·015	..	p<0·0001
Highest level of education attained										
None or primary	26 (46%)	164 (53%)	23 (14%)	114 (26%)	32 (56%)	183 (58%)	15 (42%)	61 (54%)	96 (31%)	522 (44%)
Secondary or higher	31 (54%)	145 (47%)	139 (85%)	327 (74%)	25 (44%)	132 (42%)	21 (58%)	53 (46%)	216 (69%)	657 (56%)
Missing data	..	..	1 (1%)	5 (1%)	..	..	..	..	1 (<1%)	5 (<1%)
p value	..	p=0·30	..	p=0·002	..	p=0·78	..	p=0·22	..	p<0·0001
Socioeconomic position†										
Low	33 (58%)	129 (42%)	109 (68%)	189 (42%)	28 (49%)	188 (60%)	13 (36%)	43 (38%)	183 (58%)	549 (46%)
Medium	18 (32%)	108 (35%)	38 (23%)	176 (40%)	15 (26%)	68 (22%)	13 (36%)	37 (32%)	84 (27%)	389 (33%)
High	6 (10%)	72 (23%)	15 (9%)	77 (17%)	14 (25%)	59 (19%)	10 (28%)	34 (30%)	45 (14%)	242 (20%)
Missing data	..	..	1 (1%)	4 (1%)	..	..	..	..	1 (<1%)	4 (<1%)
p value	..	p=0·035	..	p<0·0001	..	p=0·33	..	p=0·92	..	p=0·001
Area of residence										
Urban	32 (56%)	176 (57%)	..	..	15 (26%)	88 (28%)	25 (69%)	70 (61%)	72 (48%)	334 (45%)
Rural	25 (44%)	133 (43%)	..	..	42 (74%)	227 (72%)	11 (31%)	44 (39%)	78 (52%)	404 (55%)
p value	..	p=0·91	..	..	..	p=0·80	..	p=0·38	..	p=0·54
Body-mass Index (kg/m²)										
<18·5	7 (12%)	29 (9%)	9 (6%)	4 (1%)	0	14 (4%)	4 (11%)	3 (3%)	20 (6%)	50 (4%)
18·5 to <25	24 (42%)	98 (32%)	57 (35%)	54 (12%)	27 (47%)	141 (45%)	17 (47%)	43 (38%)	125 (40%)	336 (28%)
25 to <30	17 (30%)	81 (26%)	34 (21%)	91 (20%)	17 (30%)	106 (34%)	10 (28%)	30 (26%)	78 (25%)	308 (26%)
≥30	8 (14%)	87 (28%)	51 (31%)	264 (59%)	11 (19%)	48 (15%)	2 (6%)	31 (27%)	72 (23%)	430 (36%)
Missing data	1 (2%)	14 (5%)	12 (7%)	33 (7%)	2 (4%)	6 (2%)	3 (8%)	7 (6%)	18 (6%)	60 (5%)
p value	..	p=0·13	..	p<0·0001	..	p=0·34	..	p=0·013	..	p<0·0001
Cohabiting										
No	44 (77%)	211 (68%)	124 (76%)	314 (70%)	39 (68%)	167 (53%)	19 (53%)	46 (40%)	226 (72%)	738 (62%)
Yes	13 (23%)	98 (32%)	39 (24%)	132 (30%)	18 (32%)	148 (47%)	17 (47%)	68 (60%)	87 (28%)	446 (38%)
p value	..	p=0·39	..	p=0·30	..	p=0·027	..	p=0·36	..	p=0·001
Comorbidities‡										
No	35 (61%)	147 (48%)	94 (58%)	214 (48%)	47 (83%)	214 (68%)	29 (81%)	69 (60%)	205 (66%)	644 (54%)
Yes	22 (39%)	162 (52%)	69 (42%)	232 (52%)	10 (17%)	101 (32%)	7 (19%)	45 (40%)	108 (34%)	540 (46%)
p value	..	p=0·055	..	p=0·034	..	p=0·027	..	p=0·028	..	p<0·0001
Knowledge that breast cancer is curable§										
Yes	39 (68%)	238 (77%)	..	..	23 (40%)	126 (40%)	21 (58%)	80 (70%)	83 (55%)	444 (60%)
No or not known	18 (32%)	71 (23%)	..	..	34 (60%)	189 (60%)	15 (42%)	34 (30%)	67 (45%)	294 (40%)
p value	..	p=0·16	..	..	..	p=0·96	..	p=0·19	..	p=0·27
Stage at diagnosis										
I or II	21 (37%)	112 (36%)	76 (47%)	214 (48%)	13 (12%)	105 (33%)	10 (28%)	43 (38%)	120 (38%)	474 (40%)
III	30 (53%)	145 (47%)	65 (40%)	171 (38%)	28 (49%)	140 (44%)	15 (42%)	44 (39%)	138 (44%)	500 (42%)
IV	6 (10%)	52 (17%)	22 (13%)	60 (13%)	8 (14%)	52 (17%)	3 (8%)	7 (6%)	39 (13%)	171 (15%)
Unknown	..	..	0 (0%)	1 (<1%)	8 (14%)	18 (6%)	8 (22%)	20 (17%)	16 (5%)	39 (3%)
p value	..	p=0·46	..	p=0·92	..	p=0·076	..	p=0·72	..	p=0·35

(Table 1 continues on next page)

	Namibia (n=384)		South Africa (n=632)		Uganda (n=421)		Zambia (n=198)		All sites (n=1635)	
	HIV positive, n (%)	HIV negative, n (%)	HIV positive, n (%)	HIV negative, n (%)	HIV positive, n (%)	HIV negative, n (%)	HIV positive, n (%)	HIV negative, n (%)	HIV positive, n (%)	HIV negative, n (%)
(Continued from previous page)										
Tumour grade										
1	8 (14%)	48 (15%)	12 (7%)	24 (5%)	7 (12%)	62 (20%)	1 (3%)	11 (10%)	28 (9%)	145 (12%)
2	18 (32%)	114 (37%)	85 (52%)	220 (49%)	10 (17%)	51 (16%)	11 (31%)	29 (25%)	124 (40%)	414 (35%)
3	17 (30%)	67 (22%)	57 (35%)	182 (41%)	14 (25%)	68 (22%)	7 (19%)	22 (19%)	95 (30%)	339 (29%)
Not specified	14 (25%)	80 (26%)	9 (6%)	20 (5%)	26 (46%)	134 (42%)	17 (47%)	52 (46%)	66 (21%)	286 (24%)
p value	..	p=0·60	..	p=0·52	..	p=0·62	..	p=0·59	..	p=0·17
Receptor subtype¶										
Hormone receptor positive, HER2 negative	25 (44%)	150 (48%)	74 (45%)	236 (53%)	..	..	..	..	99 (45%)	386 (51%)
Hormone receptor positive, HER2 positive	17 (30%)	65 (21%)	41 (25%)	101 (23%)	..	..	..	..	58 (26%)	166 (22%)
Hormone receptor negative, HER2 positive	2 (3%)	30 (10%)	9 (6%)	22 (5%)	..	..	..	..	11 (5%)	52 (7%)
Hormone receptor negative, HER2 negative	12 (21%)	49 (16%)	33 (20%)	69 (15%)	..	..	..	..	45 (20%)	118 (16%)
Unknown	1 (2%)	15 (5%)	6 (4%)	18 (4%)	..	..	..	..	7 (3%)	33 (4%)
p value	..	p=0·20	..	p=0·34	..	..	..	..	..	p=0·11
ART use‖										
No	2 (4%)	..	44 (27%)	..	4 (7%)	..	2 (6%)	..	52 (17%)	..
Yes	53 (93%)	..	118 (72%)	..	40 (70%)	..	32 (89%)	..	243 (78%)	..
Unknown	2 (4%)	..	1 (1%)	..	13 (23%)	.	2 (6%)	..	18 (6%)	..

Data are n (%), unless stated otherwise. All p values were calculated with a χ^2 test, comparing women with HIV and HIV-negative women only. ART=antiretroviral therapy. ER=oestrogen receptor. PR=progesterone receptor. HER2=human epidermal growth factor 2. *Row percentage by HIV status includes a small number of women whose HIV status was unknown: 18 in Namibia, 23 in South Africa, 49 in Uganda, and 48 in Zambia. †Derived from a score of combined self-reported access to amenities including home ownership, indoor water, flush toilet, electricity, vehicle, refrigerator, landline, gas or electric stove, and a bed. Categories were constructed based on country-specific distribution of the score tertiles. ‡Comorbidities include non-HIV chronic conditions: tuberculosis, hepatitis, hypertension, heart disease, diabetes, anaemia, chronic obstructive pulmonary disease, asthma, other cancers, other chronic infections, and other chronic diseases. §Refers to an individual woman's knowledge (before diagnosis) that breast cancer is curable. Data on this variable were not available for South Africa because a slightly different questionnaire was used at this site. ¶Information on tumour molecular subtype was routinely available for Namibia and South Africa only. Hormone receptor positive denotes tumours that were ER positive or PR positive (or both). Hormone receptor negative denotes tumours that were ER negative and PR negative. ‖Analysis restricted to women with HIV only.

Table 1: **Patient and tumour characteristics in the ABC-DO HIV substudy, by HIV status and country**

or IV, respectively. We tested associations between patient or tumour characteristics and HIV status using χ^2 tests. We generated Kaplan-Meier curves to estimate crude 3-year survival by HIV status. A multivariable Cox proportional hazards model, stratified by country (due to varying HIV prevalence, patient profiles, catchment populations, and health systems), was used to estimate HR for HIV. We first looked at a simpler model with HIV status as the only exposure. Then, each factor (ie, age, tumour stage, tumour grade, education, socioeconomic position, and tumour receptor subtype) was added to the model to examine the change in the HR for HIV status on survival associated with each factor. Kaplan-Meier curves showed that the HIV differential was stronger after 18 months since breast cancer diagnosis than before. Therefore, as a post-hoc analysis, we performed a Lexis expansion on follow-up time up to 18 months and beyond 18 months to evaluate the HIV–time interaction and then estimated HRs for HIV based on these follow-up times respectively. We also tested the interactions between HIV status and each one of the factors (age, tumour stage, tumour grade, education, socioeconomic position, and tumour receptor subtypes), including BMI and ART use. For factors where there was evidence for interaction, we built models comparing women with HIV in each subgroup to the HIV-negative women in the comparison subgroup, to pinpoint HIV-specific differences that were independent of the effect of the characteristic itself.

In sensitivity analyses, we re-classified women with unknown HIV status as being either HIV-positive or HIV-negative (as two separate analyses), to examine whether any potential misclassification of HIV status might affect the findings. We checked all models for the validity of the proportional hazards assumption for HIV status using Schoenfeld's residuals. All analyses were done in Stata (version 16; StataCorp, College Station, TX, USA).

	Namibia (n=384)	South Africa (n=632)	Uganda (n=421)	Zambia (n=198)	All sites (n=1635)
Number of women with at least one updated vital status after baseline					
HIV negative	309	446	315	114	1184
HIV positive	57	163	57	36	313
HIV status unknown	18	23	49	48	138
Median age at diagnosis (IQR)					
HIV negative	51·7 (41·6–63·6)	58·0 (47·0–67·0)	47·0 (38·5–57·3)	50·5 (39·2–61·4)	52·4 (42·0–63·6)
HIV positive	45·2 (39·8–51·6)	45·0 (41·0–54·0)	45·3 (42·3–51·8)	44·9 (38·1–53·6)	45·2 (40·0–52·9)
HIV status unknown	57·9 (46·4–69·0)	58·0 (39·0–74·0)	48·5 (40·1–55·4)	48·0 (41·2–66·1)	50·9 (41·3–65·0)
Number of deaths at 3 years					
HIV negative	118	125	157	32	432
HIV positive	25	62	29	21	137
HIV status unknown	9	9	25	20	63
Median follow-up, years (IQR)					
HIV negative	2·8 (1·8–3·0)	1·9 (1·3–2·5)	2·3 (1·1–3·0)	1·7 (1·0–2·2)	2·1 (1·3–2·9)
HIV positive	2·8 (1·7–3·0)	1·7 (1·1–2·4)	2·2 (1·2–2·9)	1·8 (0·5–2·2)	1·9 (1·1–2·7)
HIV status unknown	2·4 (1·1–3·0)	1·2 (0·6–1·7)	2·4 (1·0–2·4)	1·5 (0·9–2·2)	1·7 (0·9–2·7)
Cumulative loss to follow-up at 3 years, n (%)					
HIV negative	8 (3%)	60 (14%)	13 (4%)	25 (22%)	106 (9%)
HIV positive	0	17 (10%)	3 (5%)	4 (11%)	24 (8%)
HIV status unknown	0	5 (22%)	4 (8%)	9 (19%)	18 (13%)
Crude 3-year survival, % (95% CI)					
HIV negative	57·6% (51·4–63·3)	63·4% (57·0–69·1)	44·6% (38·6–50·4)	65·5% (54·6–74·4)	55·4% (52·0–58·6)
HIV positive	54·6% (40·6–66·6)	46·3% (34·0–57·8)	44·4% (30·5–57·4)	26·5% (11·3–44·6)	46·3% (39·5–52·8)
HIV status unknown	42·9% (19·0–65·0)	48·1% (20·0–71·8)	43·7% (28·9–57·5)	..	42·4% (32·3–52·2)
Conditional on being alive at 18 months					
HIV negative	76·5% (70·3–81·6)	78·2% (70·8–84·0)	67·5% (60·1–73·7)	89·3% (77·4–95·1)	73·9% (70·0–77·3)
HIV positive	73·5% (57·3–84·5)	61·4% (44·7–74·5)	71·1% (51·3–84·0)	48·6% (20·1–72·3)	66·2% (57·4–73·6)
HIV status unknown	85·7% (33·4–97·9)	70·0% (22·5–91·8)	64·4% (44·7–78·6)	..	68·6% (53·7–79·6)
Among women with non-metastatic disease at diagnosis					
HIV negative	67·1% (60·3–72·9)	70·5% (63·5–76·5)	53·3% (46·4–59·8)	63·3% (50·4–73·6)	63·2% (59·4–66·7)
HIV positive	59·7% (44·7–71·8)	51·1% (37·4–63·2)	56·0% (38·3–70·5)	25·6% (8·4–47·3)	52·1% (44·4–59·2)
Among women with metastatic disease at diagnosis					
HIV negative	15·0% (6·9–26·0)	16·8% (6·7–30·7)	6·5% (2·1–14·4)	..	12·7% (7·8–18·8)
HIV positive	16·0% (5·4–9·5)	18·5% (1·6–50·4)	10·4% (0·5–37·8)	..	16·5%% (5·5–32·7)

Table 2: **ABC-DO HIV substudy follow-up, deaths, and crude 3-year overall survival estimates by HIV status and country**

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis and interpretation, writing of the report, or in the decision to submit it for publication.

Results

Between Sept 8, 2014, and Dec 31, 2017, we recruited 2154 women with primary breast cancer, of whom 332 (15%) were HIV positive, 1608 (75%) were HIV negative, and 214 (10%) had an unknown HIV status. Due to small numbers of women with HIV in Nigeria (12 [3%] *vs* 374 HIV negative or unknown) and in non-Black groups in Namibia (three [3%] *vs* 94) and South Africa (four [11%] *vs* 32), these patient groups (519 women) were excluded from the analysis. We enrolled 1635 Black women from Namibia (n=384), South Africa (n=632), Uganda (n=421), and Zambia (n=198).

Of the 169 women considered to be positive for HIV from ABC-DO study sites where HIV status was self-reported, 130 (77%) had concordant HIV self-report in both questionnaires (median 31 days apart [IQR 6–113]), 20 (12%) had a HIV-positive self-report in the presenting symptoms questionnaire only, and 19 (11%) in the baseline interview only. Data on CD4 count and HIV RNA were largely missing, except for women in South Africa. Data on receptor status were largely missing in Uganda and Zambia due to either unavailability of immunohistochemistry testing or patients being unable to cover the costs. Thus, analyses on receptor status were restricted to Namibia and South Africa.

Among women included in the present analysis, the overall HIV prevalence was 19% (313 of 1635) but ranged from 14% (57 of 421) in Uganda to 26% (163 of 632) in South Africa (table 1; ie, representing the countries

	Namibia		South Africa		Uganda		Zambia		All sites		All sites, up to 18 months of follow-up		All sites, if alive at 18 months	
	Deaths, n	HR (95% CI)	Deaths, n	HR (95% CI)	Deaths, n	HR (95% CI)	Deaths, n	HR (95% CI)	Deaths, n	HR (95% CI)	Deaths, n	HR (95% CI)	Deaths, n	HR (95% CI)
Crude														
HIV negative	118	1 (ref)	125	1 (ref)	157	1 (ref)	32	1 (ref)	432	1 (ref)	269	1 (ref)	163	1 (ref)
HIV positive	25	1·14 (0·74–1·76)	62	1·47 (1·09–2·00)	29	1·09 (0·73–1·61)	21	2·23 (1·29–3·87)	137	1·35 (1·11–1·63)	87	0·95 (0·74–1·22)	50	1·40 (1·02–1·93)
Age														
HIV negative	118	1 (ref)	125	1 (ref)	157	1 (ref)	32	1 (ref)	432	1 (ref)	269	1 (ref)	163	1 (ref)
HIV positive	25	1·23 (0·79–1·92)	62	1·67 (1·20–2·31)	29	1·14 (0·76–1·70)	21	2·87 (1·57–5·25)	137	1·46 (1·19–1·78)	87	0·99 (0·77–1·28)	50	1·48 (1·06–2·06)
Stage														
HIV negative	118	1 (ref)	125	1 (ref)	157	1 (ref)	32	1 (ref)	432	1 (ref)	269	1 (ref)	163	1 (ref)
HIV positive	25	1·39 (0·88–2·19)	62	1·58 (1·14–2·20)	29	1·10 (0·73–1·66)	21	3·12 (1·66–5·87)	137	1·46 (1·19–1·79)	87	0·97 (0·75–1·27)	50	1·53 (1·09–2·15)
Other factors*														
HIV negative	118	1 (ref)	123	1 (ref)	157	1 (ref)	32	1 (ref)	430	1 (ref)	266	1 (ref)	163	1 (ref)
HIV positive	25	1·26 (0·79–2·03)	61	1·61 (1·14–2·28)	29	1·09 (0·72–1·65)	21	3·10 (1·64–5·88)	136	1·41 (1·15–1·74)	85	0·98 (0·75–1·29)	50	1·48 (1·06–2·08)
Receptor subtypes														
HIV negative	112	1 (ref)	120	1 (ref)	..	..	..	..	232	1 (ref)	141	1 (ref)	91	1 (ref)
HIV positive	25	1·36 (0·84–2·20)	59	1·54 (1·08–2·20)	..	..	..	..	84	1·43 (1·08–1·88)	50	1·22 (0·83–1·79)	34	1·56 (1·01–2·40)

Data were adjusted to a simple model with HIV status as the only exposure, each of the other factors were added sequentially to the model one at a time (ie, age, then stage). HR=hazard ratio. *Other factors include tumour grade, highest level of education attained, and socioeconomic position.

Table 3: **Adjusted hazard ratios (stratified by country) for the association between HIV status and 3-year survival, 18-month survival, and 3-year survival conditional on surviving the first 18 months for all ABC-DO sites**

where HIV prevalence in Black African women was over 10%). Age at breast cancer diagnosis, socioeconomic position, educational level attained, BMI, cohabitation status, and presence of other comorbidities were all associated with HIV status. Women with HIV were younger at breast cancer diagnosis than their HIV-negative counterparts (table 1). The percentage of women with HIV who were overweight or obese was lower than among HIV-negative women. Most women with HIV were on ART. Cancer stage, grade, and receptor subtypes at diagnosis were not associated with HIV status (table 1). The proportion of late-stage (TNM III and IV) breast cancer at diagnosis was high, but was similar among women with HIV and HIV-negative women for all countries combined and for each country individually (table 1). The proportion of women with triple-negative breast tumours was also similar between women with and without HIV in Namibia and South Africa, where immunohistochemistry testing was routinely available.

Of the 1635 women who were followed up for up to 3 years, 632 (39%) died, 44% (137 of 313) of whom had HIV and 37% (432 of 1184) did not, 855 (52%) were alive at 3 years, and 148 (9%) were censored early (statistical loss to follow-up; table 2). The crude overall survival at 3 years for all sites combined was 46% (95% CI 40–53) in women with HIV versus 55% (52–59) in HIV-negative women. The crude HR for the difference in all-cause mortality between women with and without HIV was 1·35 (95% CI 1·11–1·63) for all ABC-DO sites combined, but this value varied across sites (table 3). Absolute differences in 3-year overall survival estimates between women with and without HIV of at least 15% were seen in South Africa and Zambia, compared with 9% in Namibia and less than 1% in Uganda. In Uganda, women with HIV experienced lower mortality rates within the first 6 months of diagnosis than did HIV-negative women, but higher mortality rates thereafter (figure 1). Relative to the other ABC-DO sites, the finding that survival did not differ by HIV status in Uganda does not necessarily mean a better survival experience in women with HIV in this country, but rather that women with and without HIV experienced particularly low survival (appendix p 5). Lower survival was also seen in the small proportion of women with unknown HIV status compared with HIV-negative women (table 2).

The differences by HIV status became marginally stronger when adjusted for relevant patient and tumour characteristics (adjusted HR [aHR] 1·41, 95% CI 1·15–1·74), including tumour receptor subtypes which were available in Namibia and South Africa only (aHR 1·43, 1·08–1·88 *vs* corresponding crude HR 1·35, 1·05–1·72 for these two countries). Based on observed steeper survival curves in women with HIV beyond

18 months (figure 1), follow-up time was split at 18 months. Absolute survival differences by HIV status were modest within the first 18 months of follow-up (figure 1, table 2), but became more marked beyond 18 months (table 2). The relative HIV differentials were stronger after 18 months of follow-up (crude HR 1·40, 95% CI 1·02–1·93) than within the first 18 months of follow-up (0·95, 0·74–1·22; $p_{interaction}$=0·06). When restricted to women with non-metastatic disease at diagnosis (stages I–III), the magnitude of the HIV differential for overall 3-year all-cause mortality (adjusted for age, stage, and grade) increased from 1·52 (1·24–1·87) to 1·64 (1·29–2·09; appendix pp 5, 8). Among women with non-metastatic disease, the HIV differential was stronger for individuals who survived beyond the first 18 months (adjusted HR 1·58, 1·09–2·28; appendix p 5) than for those alive within the first 18 months (1·05, 0·75–1·46). There were no differences by HIV status among women with metastatic disease (adjusted HR 1·10, 0·70–1·73) even when restricted to those alive beyond 18 months (1·14, 0·42–3·11; appendix p 5). However, the absolute difference in survival percentage between women with and without HIV was consistent at all stages (table 2). Therefore, the observed HIV–time interaction was not due to early deaths among women with metastatic disease, but rather points to a real strengthening of the HIV differential over time.

Figure 2 shows survival differences by HIV status according to patient and tumour characteristics. The increased all-cause mortality among women with HIV differed by tumour stage at diagnosis ($p_{interaction}$=0·06) and ART (p=0·0001) only. Relative to their HIV-negative counterparts of the same stage, women with HIV with tumour stages I or II and tumour stage III had, respectively, increases of 58% (aHR 1·58, 95% CI 0·98–2·57) and 73% (aHR 1·73, 1·31–2·28) in all-cause mortality, whereas women with HIV with stage IV disease had similar all-cause mortality as HIV-negative women (aHR 1·10, 0·70–1·73). Overall, among women with non-metastatic breast cancer, those with HIV had an increase of 65% (aHR 1·65, 1·30–2·10) in all-cause mortality compared with HIV-negative women of the same stage.

Women with HIV had increased all-cause mortality compared with their HIV-negative counterparts of the same tumour stage (appendix p 9). The magnitude of this increase corresponded to a single shift in stage (eg, women with HIV with stage IIB breast cancer had mortality rates almost reaching those for HIV-negative women with stage IIIA breast cancer), with the exception

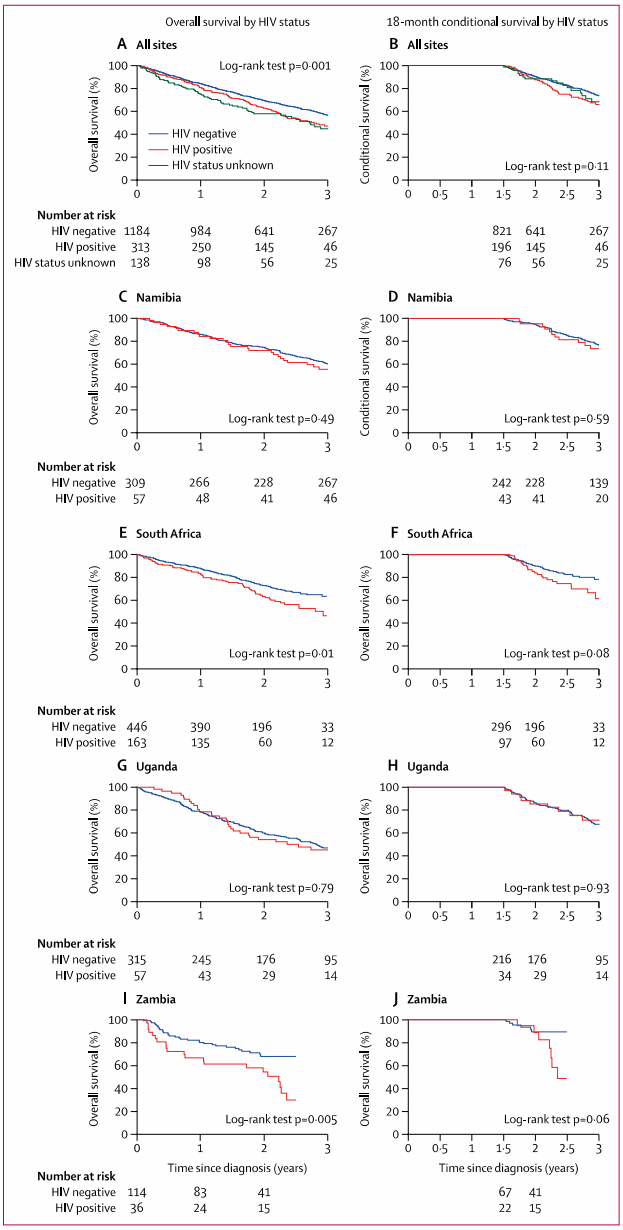
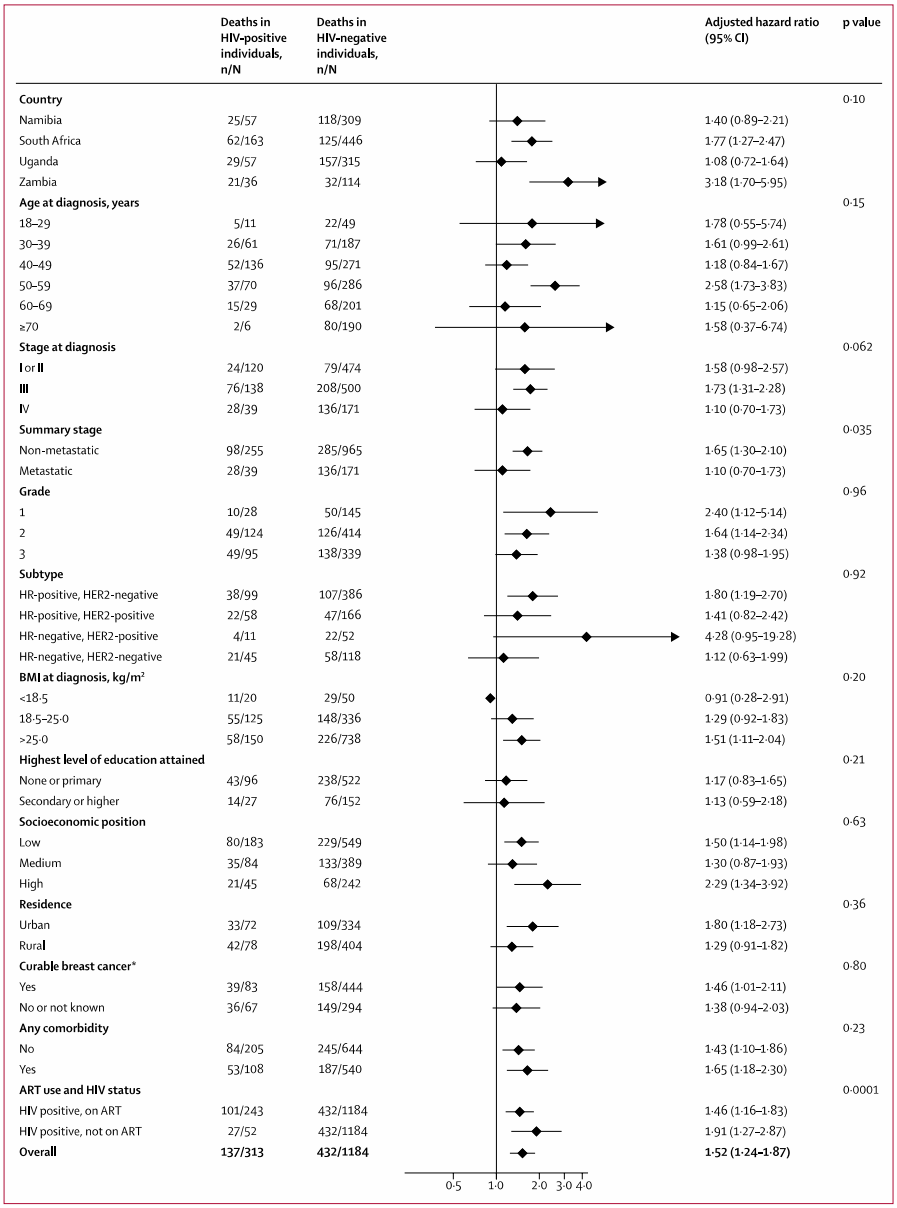


Figure 1: **Kaplan-Meier curves for 3-year overall survival and 18-month conditional survival after breast cancer diagnosis, by HIV status in the ABC-DO HIV substudy**

The number of participants at time 0 reflects the number of women at enrolment, but their contribution to time at risk might have commenced a short time later as per date of baseline interview.



	Deaths in HIV-positive individuals, n/N	Deaths in HIV-negative individuals, n/N	Adjusted hazard ratio (95% CI)	p value
Country				0·10
Namibia	25/57	118/309	1·40 (0·89–2·21)	
South Africa	62/163	125/446	1·77 (1·27–2·47)	
Uganda	29/57	157/315	1·08 (0·72–1·64)	
Zambia	21/36	32/114	3·18 (1·70–5·95)	
Age at diagnosis, years				0·15
18–29	5/11	22/49	1·78 (0·55–5·74)	
30–39	26/61	71/187	1·61 (0·99–2·61)	
40–49	52/136	95/271	1·18 (0·84–1·67)	
50–59	37/70	96/286	2·58 (1·73–3·83)	
60–69	15/29	68/201	1·15 (0·65–2·06)	
≥70	2/6	80/190	1·58 (0·37–6·74)	
Stage at diagnosis				0·062
I or **II**	24/120	79/474	1·58 (0·98–2·57)	
III	76/138	208/500	1·73 (1·31–2·28)	
IV	28/39	136/171	1·10 (0·70–1·73)	
Summary stage				0·035
Non-metastatic	98/255	285/965	1·65 (1·30–2·10)	
Metastatic	28/39	136/171	1·10 (0·70–1·73)	
Grade				0·96
1	10/28	50/145	2·40 (1·12–5·14)	
2	49/124	126/414	1·64 (1·14–2·34)	
3	49/95	138/339	1·38 (0·98–1·95)	
Subtype				0·92
HR-positive, HER2-negative	38/99	107/386	1·80 (1·19–2·70)	
HR-positive, HER2-positive	22/58	47/166	1·41 (0·82–2·42)	
HR-negative, HER2-positive	4/11	22/52	4·28 (0·95–19·28)	
HR-negative, HER2-negative	21/45	58/118	1·12 (0·63–1·99)	
BMI at diagnosis, kg/m²				0·20
<18·5	11/20	29/50	0·91 (0·28–2·91)	
18·5–25·0	55/125	148/336	1·29 (0·92–1·83)	
>25·0	58/150	226/738	1·51 (1·11–2·04)	
Highest level of education attained				0·21
None or primary	43/96	238/522	1·17 (0·83–1·65)	
Secondary or higher	14/27	76/152	1·13 (0·59–2·18)	
Socioeconomic position				0·63
Low	80/183	229/549	1·50 (1·14–1·98)	
Medium	35/84	133/389	1·30 (0·87–1·93)	
High	21/45	68/242	2·29 (1·34–3·92)	
Residence				0·36
Urban	33/72	109/334	1·80 (1·18–2·73)	
Rural	42/78	198/404	1·29 (0·91–1·82)	
Curable breast cancer*				0·80
Yes	39/83	158/444	1·46 (1·01–2·11)	
No or not known	36/67	149/294	1·38 (0·94–2·03)	
Any comorbidity				0·23
No	84/205	245/644	1·43 (1·10–1·86)	
Yes	53/108	187/540	1·65 (1·18–2·30)	
ART use and HIV status				0·0001
HIV positive, on ART	101/243	432/1184	1·46 (1·16–1·83)	
HIV positive, not on ART	27/52	432/1184	1·91 (1·27–2·87)	
Overall	**137/313**	**432/1184**	**1·52 (1·24–1·87)**	

0·5 1·0 2·0 3·0 4·0

Figure 2: **Hazard ratios for 3-year all-cause mortality in HIV-positive *vs* HIV-negative women with breast cancer, by patient and tumour characteristics in the ABC-DO HIV substudy (all sites combined)**

Hazard ratios were adjusted for age, tumour stage, and tumour grade at breast cancer diagnosis. p value for interaction between HIV status and each patient and tumour variable listed. ART=antiretroviral therapy. BMI=body-mass index. HR=hormone receptor. *Refers to a woman's knowledge of whether breast cancer is curable if detected early.

of women with stage IV (ie, metastatic disease). Relative to HIV-negative women, women with HIV not on ART had poorer survival (aHR 1·91, 95% CI 1·27–2·87) than did women with HIV on ART (1·46, 1·16–1·83; figure 2). There was no clear evidence that the HIV differential was modified by BMI or tumour receptor subtypes, although women with HIV who were overweight or obese (aHR 1·51, 1·11–2·04), and those with hormone receptor-positive or HER2-negative tumours (1·80, 1·19–2·70), had increased all-cause mortality, but estimates were based on small numbers. There were small differences in the adjusted HR for HIV among women with non-metastatic disease for the different assumptions on HIV unknowns: 1·55 (1·26–1·91) if assumed HIV positive; 1·60 (1·26–2·03) if HIV negative; and 1·63 (1·29–2·09) if dropped from the analysis (appendix p 6).

Discussion

In this large, prospective, multi-country ABC-DO study in sub-Saharan Africa, women living with HIV who were diagnosed with breast cancer, particularly those with non-metastatic disease, experienced increased all-cause mortality relative to their HIV-negative counterparts, with the effect persisting upon adjustment for other relevant prognostic factors. However, differences by HIV status were more pronounced in some settings than others. In Zambia, women with HIV had higher risk of mortality than HIV-negative women. In Uganda, 3-year overall survival was very low, regardless of HIV status, and most women presented with late-stage disease.

Similar to other studies in the region[7,10,27,28] and elsewhere[3,12,14] women with HIV in the ABC-DO cohort were diagnosed with breast cancer at younger ages than were HIV-negative women, given that women with HIV are younger than the general population. Similar to other studies,[10,28] albeit not all,[7,17,29] our study found that the prevalence of late-stage breast cancer at diagnosis did not differ by HIV status. However, women with HIV had increased risk of mortality than did HIV-negative women for the same tumour stage, with the relative HIV differential being stronger among those with non-metastatic disease at diagnosis (65% increased mortality risk). A study in the USA reported comparable overall survival by HIV status between women with stage I–III tumours only and all women (stages I–IV), but the proportion of women with metastatic disease was small.[17] Although on this scale of analysis the relative increase in mortality was stronger in women with non-metastatic disease than in those with metastatic disease, it remains possible that the absolute difference in mortality rates between women with and without HIV is constant at all stages and this constant difference would represent a smaller relative increase (more difficult to detect) in women with metastatic disease. Excess bodyweight is associated with poor survival from breast cancer.[19] We found no evidence that the HIV differential was modified by BMI. However, the difference in all-cause mortality between women with and without HIV was stronger among overweight or obese women. These findings are consistent with reports of increased risk of obesity and increased risk of, and mortality from, cardiovascular diseases among women with HIV on ART.[20] Although women with HIV on ART had poor survival outcomes compared with HIV-negative women, they had better survival outcomes than did women with HIV who were not on ART, emphasising the importance of ART adherence on cancer survival.[11]

Studies in the USA have shown that both overall and breast cancer-specific survival is poor in women with HIV (*vs* HIV-negative women) even after adjusting for stage at diagnosis and type of cancer treatment received.[12,14,17] To date, no such studies have been conducted in sub-Saharan Africa. Our finding that the HIV differential was stronger in women with non-metastatic disease and manifested only beyond 18 months follow-up suggests that the excess deaths in women with HIV were not due to immediate treatment-related toxicity but rather point to a longer term treatment pathway or differential, highlighting the importance of early diagnosis and timely access to effective breast cancer and HIV treatments among women with HIV. More consideration should be given to the feasibility and effectiveness of integrating breast cancer care into existing functional HIV or cervical cancer services through the promotion of breast cancer awareness among women with HIV and their health-care workers, coupled with implementation of efficient patient navigation systems to minimise delays in cancer diagnosis and initiation of treatment, and minimise disruptions and abandonment of cancer or HIV treatments. Our findings underscore the need for standard clinical guidelines on how best to simultaneously manage the two conditions. Previously, we reported that women with HIV were less likely (*vs* HIV-negative women) to receive curative treatment for breast cancer within the first 12 months of diagnosis,[30] either due to scarcity of oncologists or expertise on how to co-manage both diseases, particularly in Zambia and Uganda. Furthermore, the absence of universal free health care and increased out-of-pocket costs of cancer care might have resulted in long delays to cancer treatment initiation and to interruptions and abandonment of HIV or cancer treatments.

The strengths of this study include its large size, the considerable proportion (19%) of women with HIV, the prospective multi-country design, the collection of detailed clinical and epidemiological data, and the use of an mHealth application to minimise losses to follow-up.

This study has several limitations. First, self-reported HIV status might have led to non-differential exposure misclassification and underestimation of the effect of HIV status on survival. However, the high percentage (>50%) of women with HIV tested in South Africa, high level of within-woman agreement on HIV

self-reports taken at two distinct timepoints, and consistency of the findings across the different settings indicate that misclassification of self-reported HIV status was probably minimal. Sensitivity analyses also showed that any potential misclassification of HIV status would have had little effect on the findings. Second, the high proportion of missing data for CD4 count and viral load and the absence of data on HIV stage and management history prevented examination of whether severity of HIV/AIDS contributed to the poorer survival outcomes seen among women with HIV. We could not examine whether survival differences vary by HIV-1 versus HIV-2 types due to the absence of such data and the exclusion of women from Nigeria, west Africa (where HIV-2 is most prevalent) due to low HIV prevalence (<4%). Third, the absence of data on cause of death precluded examination of cause-specific survival differential by HIV status. Lastly, the hospital-based nature of ABC-DO might limit the generalisation of study findings.

In summary, this ABC-DO study showed that women with HIV had lower survival outcomes at 3 years post-diagnosis for breast cancer than their HIV-negative counterparts, even after taking into account other prognostic factors assessed at diagnosis. To prevent deaths in this patient group a better understanding is needed of the reasons for and the extent to which survival differentials by HIV status in sub-Saharan Africa reflect underlying biological mechanisms, differential access to (or compliance with) appropriate treatment regimens, detrimental HIV–breast cancer treatment interactions, or simply increased background mortality associated with HIV.

Contributors

SC led the statistical analysis and drafted the manuscript, under guidance of VM and Id-S-S. VM, Id-S-S, JS, AZ, AA, MG, GP, HC, MJ, LFP, and MF designed and conducted the study, and contributed to the interpretation of the results and the writing of the manuscript. VM, PB, MF, and MJ accessed and verified the underlying data. The corresponding author had the final responsibility for the decision to submit for publication. All authors have read and approved the submitted version of the article.

Declaration of interests

We declare no competing interests.

Data sharing

ABC-DO study data, including on individual participants, are available and can be accessed at the International Agency for Research on Cancer through collaborative work. Requests should be made to env@iarc.fr.

Acknowledgments

The ABC-DO study was sponsored by Susan G Komen (grants IIR13264158, GSP18IARC001, and GSP19IARC001), the National Cancer Institute (grants R01CA244559 and R01CA250012), and the International Agency for Research on Cancer Branch of Environmental and Lifestyle Epidemiology. The work reported in this paper was undertaken as part of PhD research of SC supported by the UK-Commonwealth Scholarships. Where authors are identified as personnel of the International Agency for Research on Cancer (IARC) or WHO, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of IARC or WHO. We thank the participants, their families, and the study interviewers for taking part in the study. This paper is dedicated to the memory of our colleague, Prof Charles A Adisa, who was the founder of the ABC-DO study in Abia, Nigeria.

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6.3 Summary

- This chapter examined disparities in overall survival after a breast cancer diagnosis between HIV-infected and HIV-uninfected women in a large, prospective, multi-country ABC-DO study in SSA. Three-year overall survival was 9% lower in HIV-infected women with breast cancer than in HIV-uninfected women with breast cancer.
- HIV-infected women with breast cancer had 41% increased risk of all-cause mortality compare with HIV-uninfected women with breast cancer even after adjusting for patient and tumour characteristics including stage at diagnosis (adjusted HR 1.41, 95% CI 1.15-1.74) and tumour molecular subtypes (in South Africa only)- adjusted HR 1.43 (1.08-1.88).
- Although the distribution of tumour characteristics at cancer diagnosis (e.g., stage) did not differ by HIV status, the relative HIV differential was much stronger among women with non-metastatic (stage I-III) i.e., among women of the same stage I-III, HIV infected women had 65% increased risk of all-cause mortality than did HIV-uninfected women.
- One of the limitations of the study was its use of self-reported HIV status in most of ABC-DO sites which might have led to non-differential exposure misclassification and underestimation of the effect of HIV status on survival. However, >50 of HIV-infected women came from South Africa where testing was done; there was a high level of within-woman agreement on HIV self-reports taken at two distinct time points; the consistency of results across all settings indicate that misclassification of HIV status was minimal; and sensitivity analyses were conducted which showed little effect on findings.
- A better understanding of reasons for the higher all-cause mortality in HIV-infected women with breast cancer, including the potential differences in background mortality between HIV-infected and HIV-uninfected women (i.e., HIV-infected women may have increased background mortality due to HIV/AIDS deaths) is needed if early deaths in unique patient population are to be prevented.

Chapter 7 Relative (net) survival for HIV-infected women with breast cancer relative to HIV-uninfected breast cancer women

7.1 Introduction

In chapter 6, using data from the ABC-DO study, I estimated the overall survival following a breast cancer diagnosis in HIV-infected women relative to their HIV-uninfected women with breast cancer. I also examined whether prognostic factors (such as age, stage, receptor status and body mass index (BMI)) explain the lower survival experience in HIV-infected women and explored how the HIV differential varies across different patient groups and settings in sub-Saharan Africa (SSA). One of the probable reasons for increased risk of all-cause mortality in HIV-infected women (vs. HIV-uninfected women) with breast cancer may be because of higher background mortality due to HIV/AIDS deaths. Therefore, I conducted analyses estimating relative (net) survival i.e., taking into account differences in background mortality between HIV-infected and HIV-uninfected women with breast cancer using data from ABC-DO study and life tables generated from UNAIDS mortality estimates. This chapter is also presented as research paper 3 and has been prepared for submission to the International Journal of Cancer.

7.2 Research paper 3

The role of HIV/AIDS-associated mortality on disparities in all-cause mortality between HIV-infected and HIV-uninfected breast cancer patients in the multi-country ABC-DO cohort

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed <u>for each</u> research paper included within a thesis.

SECTION A – Student Details

Student ID Number	LSH396778	**Title**	Mr.
First Name(s)	Steady Jerome Dickson		
Surname/Family Name	Chasimpha		
Thesis Title	Breast cancer in women living with HIV in Sub-Saharan Africa: presentation, diagnosis, and survival		
Primary Supervisor	Prof. Isabel dos-Santos-Silva		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

<u>SECTION B – Paper already published</u>

Where was the work published?	N/A		
When was the work published?	N/A		
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<u>SECTION C – Prepared for publication, but not yet published</u>

Where is the work intended to be published?	International Journal of Cancer
Please list the paper's authors in the intended authorship order:	Steady Chasimpha, Valerie Mccormack, Herbert Cubasch, Maureen Joffe, Annelle Zietsman, Moses Galukande, Groesbeck Parham, Leeya F Pinder, Isabel dos-Santos-Silva
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the first and corresponding author. I co-designed the analysis, conducted the analysis, and led the writing of the manuscript.

SECTION E

Student Signature	[redacted]
Date	21 October 2023

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Date	23 October 2023

Title: The role of HIV/AIDS-associated mortality on disparities in all-cause mortality between HIV-infected and HIV-uninfected breast cancer patients in the multi-country ABC-DO cohort

Short title: HIV/AIDS-associated mortality and all-cause mortality in HIV-infected vs. HIV-uninfected breast cancer patients

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Abstract

HIV-infected women with breast cancer have worse overall survival than their HIV-uninfected counterparts with breast cancer. We examined whether higher background mortality rates associated with HIV/AIDS significantly contribute to the higher all-cause mortality observed in HIV-infected breast cancer patients in the African Breast Cancer-Disparities in Outcomes (ABC-DO) study. Women with a newly diagnosed breast cancer completed a baseline interview (including self-reported or tested HIV status) and were actively followed-up via telephone calls every 3 months. We estimated 3-year overall and relative (net) survival accounting for country and HIV-status specific background mortality for age, and corresponding hazard ratios for HIV, adjusting for age and stage at cancer diagnosis, using flexible proportional mortality models. In all, 1940 women with known HIV status were included, of whom 312 (Nigeria), 131 (non-Black ethnicity) and 407 women aged >60 years were excluded due to small numbers of HIV-infected women for comparison. Among the remaining 1090 women, 284 (26%) were HIV-infected; 51 (19%) from Namibia; 146 (36%) South Africa; 51 (17%) Uganda; and 36 from (30%) Zambia. At the end of follow-up (January 1, 2019), a higher proportion of HIV-infected (123 (43%)) than HIV-uninfected women (290 (36%)) had died. 3-year relative survival was 10% absolute percentage points lower among HIV-infected (49%; 95% CI 42-57%) than among HIV-uninfected women (59%; 55-64%). There was only a slight difference between mortality rate ratios from overall and relative survival methods (hazard ratio: 1.41 (1.13-1.75) vs. 1.38 (1.09-1.76) respectively), indicating that the observed survival disparity was not greatly affected by higher background mortality associated with HIV/AIDS in HIV-infected patients. Further, more granular studies are needed to investigate cancer-HIV treatment interactions and their implications on survival.

Novelty and Impact

Women with HIV diagnosed with breast cancer experience higher mortality than their HIV-uninfected counterparts with breast cancer, yet the reasons underlying this survival disparity remain unclear. In this multi-country African Breast Cancer-Disparities in Outcomes (ABC-DO) cohort, HIV-infected patients had lower 3-year relative survival than HIV-uninfected patients, with slight differences between overall and relative survival estimates suggesting a minimal contribution of the higher background mortality associated with HIV/AIDS to the increased mortality in HIV-infected patients in sub-Saharan Africa.

Key words

Breast cancer, HIV, survival, Africa, excess mortality

List of abbreviations

ABC-DO	African Breast Cancer-Disparities in Outcomes study
AJCC	American Joint Committee on Cancer
AIDS	Acquired immune deficiency syndrome
CI	Confidence interval
HER2	Human Epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HR	Hazard ratio
IeDEA	International epidemiology databases to evaluate AIDS
IQR	Interquartile range
SSA	Sub-Saharan Africa
UNAIDS	The joint United Nations programme on HIV/AIDS
US	United States

Article category: Cancer Epidemiology

Introduction

With the increased access to potent antiretroviral therapy (ART) for HIV, the life expectancy in women with HIV has greatly improved[1]. Consequently, diseases whose incidence rates rise with age, including different types of non-AIDS defining cancers such as breast cancer, are becoming an increasingly important burden in this population[2-4]. HIV-infected patients are not at increased risk of breast cancer compared to HIV-uninfected women. However, breast cancer is a commonly diagnosed cancer in HIV-infected patients as it is in all women globally[2,4]. When a HIV-infected woman does develop breast cancer, unfortunately she will experience lower overall survival than breast cancer patients who are HIV-uninfected[5-8]. Reports from sub-Saharan Africa, a region with the highest population of HIV-infected patients, found that HIV-infected women with breast cancer experience between 40-70% higher all-cause mortality rates relative to HIV-uninfected breast cancer patients even after adjustment for differences in patient and tumour characteristics[5-7,9,10].

The reasons underlying these observed survival disparities remain unclear. We previously described potential pathways leading to higher all-cause mortality (lower overall survival) in HIV-infected breast cancer patients compared to HIV-uninfected counterparts[11]. Theoretically, the higher all-cause mortality rates in HIV-infected patients may be due to higher breast cancer-specific mortality rates in HIV-infected patients than in patients without HIV if patients with HIV have more aggressive breast tumour characteristics or have poor access and/or adherence to standard treatment or experience intensified adverse effects and HIV-cancer drug-to-drug interactions. Alternatively or additionally, HIV-infected patients are expected to have higher non-breast cancer deaths than HIV-uninfected patients owing to their higher background mortality than women in the general population (due to AIDS and non-AIDS mortality), and in addition to this, further excess of non-breast cancer deaths than women with HIV only due to other non-breast cancer causes (e.g., psychological distress, suicide, and challenges of adherence to HIV treatment during cancer treatment).

In the US, Coghill et al.[12] found excess all-cause and breast cancer-specific mortality rates in patients with HIV and breast cancer particularly among those who were non-white and below age 70 years of age. Other studies in the US have also shown that breast cancer-specific mortality remains higher in HIV-infected compared with HIV-uninfected women with breast cancer (adjusted hazard ratios ranging from 1.85 to 2.84)[13-15]. There have been no similar studies in SSA due to lack of cause-specific mortality data[16,17]. Besides, even in countries that have such data, such as the US, it can be difficult to determine the underlying cause of death in patients with more than one serious condition leading to misclassification of AIDS deaths as due to cancer or vice-versa. To overcome the difficulties in ascertaining the true

underlying cause of death in cancer patients, relative survival methods have been widely used. These methods model the excess mortality rate as the difference between all-cause mortality rate in the cancer patients under study and the expected all-cause mortality rate of a comparable cancer-free group from the general population[18]. Thus, relative survival methods do not require information on cause of death. The expected mortality rate is based on suitable nationwide population lifetables ideally for the appropriate subset of the population (e.g., by ethnicity, social class, HIV status) if available.

The African Breast Cancer-Disparities in Outcomes (ABC-DO) study is a multi-country prospective cohort of newly diagnosed breast cancer patients in SSA[19]. We previously reported that HIV-infected women in ABC-DO were at higher risk of dying within 3 years of their cancer diagnosis than their HIV-uninfected counterparts even after adjusting for age, tumour grade and stage at diagnosis, and other relevant factors[5,7]. In the present study, we estimated net survival in HIV-infected and HIV-uninfected ABC-DO women, using relative survival methods, to examine whether the especially higher background mortality associated with HIV significantly contributes to the previously reported higher mortality in HIV-infected breast cancer patients.

Materials and Methods

From September 2014 to December 2017, the ABC-DO study recruited women (aged ≥18 years) newly diagnosed with breast cancer (>80% histologically or cytologically conformed) in five countries in SSA with varying HIV prevalence: Namibia (11%), South Africa (17.8%), and Zambia (10.8%) in southern Africa where HIV prevalence is high, Uganda (5.1%) in east Africa where HIV prevalence is intermediate, and Nigeria (2.1%)[20] in west Africa where HIV prevalence is low. The ABC-DO study was approved by the ethics committees of all institutions involved (appendix 1). All participants provided written or thumbprint informed consent before recruitment.

As per published protocol[19], participants completed an interviewer-administered baseline questionnaire, consented to use of clinical records and tumour blocks and to be actively followed up via telephone interviews every 3 months. The questionnaire collected detailed data on patient and socio-demographic factors, including age, education level, marital status, cohabitation status (yes/no), residential area (urban/rural), access to nine household amenities use to generate site-specific tertiles of socio-economic position, breast cancer awareness, HIV status and presence of other non-HIV chronic comorbidities. Participants were tested for HIV infection in South Africa, but HIV infection status was self-reported in all other countries on baseline interview and on presenting symptoms questionnaire. Thus, a

woman was considered HIV-positive if responses were positive on either questionnaire. Details of HIV and HIV-related data in ABC-DO study have been published previously[5]. Clinical data were extracted from medical records using standard pro-forma. These included breast cancer stage at diagnosis (according to the American Joint Committee on Cancer (AJCC) TNM staging system), tumour grade and tumour receptor status (oestrogen-, progesterone-status, and HER2- expression (positive or negative) if documented. Oestrogen-positivity and progesterone-positivity were defined as at least 1% immunohistochemistry staining for their receptor, and HER2-positivity as an immunohistochemistry score of 3 by immunohistochemistry or a positive fluorescence in-situ hybridisation result.

Outcomes

In the present analyses, the primary outcome was 3-year overall (based on all-cause mortality) survival, which was analysed for all women with at least one updated vital status after baseline interview. Vital status was ascertained via a telephone interview to the participant, or their next of kin once every three months, and during woman's routine visits to participating hospital for clinical management. The ABC-DO data collection and follow up protocols were implemented using a tailored mobile health application.

Statistical methods

We estimated 3-year overall survival on a time since breast cancer diagnosis scale, with at-risk time defined from the latest of either date of cancer diagnosis or ABC-DO recruitment if later (i.e. left-censoring) to the earliest of: date of death from any cause, date last known alive or administrative censoring on the earliest of 3 years post-diagnosis or 1 January 2019. Crude Kaplan Meier survival curves were constructed for both overall and net survival by HIV status, separately for each country and for all countries combined.

We calculated net survival (stns in Stata), accounting for background mortality differences between breast cancer women with and without HIV, under the relative survival framework. Relative survival is calculated as the ratio of observed overall survival of the patients to the expected survival of a similar population without the condition in the general population[18,21]. Expected survival is usually estimated from nationwide population life tables stratified by relevant variables (e.g., age, sex and calendar year). However, there are no readily available HIV-specific life tables in sub-Saharan Africa and hence we used mortality estimates from the Joint United Nations Programme on HIV/AIDS (UNAIDS) to create age-, calendar year- and HIV-specific lifetables for women in each ABC-DO participating country. Every year, the

UNAIDS publishes updated global, regional- and country-specific HIV data including modelled AIDS-related mortality estimates as part of monitoring the progress and state of the AIDS epidemic. Details of how these estimates are modelled have been previously published[22-25]. We obtained age-specific AIDS-related deaths of HIV-positive women in the population and all-cause deaths of HIV-negative women from UNAIDS and estimated all-cause mortality rates in women with and without HIV, for Namibia, South Africa, Zambia, and Uganda for the study period (2014-2020) as below:

If HIV-uninfected: Rate 0 = all-cause mortality rate in HIV-uninfected women

If HIV-infected: Rate 1 = all-cause mortality rate in HIV-uninfected women + AIDS-related mortality rate

These were then used to create complete life tables by 1-year age group, country, and HIV status (positive or negative).

We used multivariable Cox proportional hazards models, to estimate all-cause hazard ratios (HR) for HIV, and then flexible parametric survival models (stpm2 in Stata), which employ restricted cubic splines, to estimate excess HRs for HIV accounting for age-country-HIV specific mortality as described above. All models were stratified by country (due to varying HIV prevalence and other factors) and adjusted for age, and tumour stage at diagnosis. We checked all models for Cox proportional hazards assumptions using Schoenfeld's residuals. All analyses were performed in Stata (version 16; Stata Corp, College Station, TX, USA).

Results

In all, there were 1940 ABC-DO women with a known HIV status, of whom 332 (17.1%) were HIV positive. Patients from Nigeria (N=312) as well as those of non-Black ethnicity in Namibia (95) and South Africa (36) were excluded due to small numbers of HIV-infected women (12 (4%), 3 (3%) and 4 (11%), respectively). In all study sites, HIV-infected patients with breast cancer were much younger than HIV-uninfected patients with breast cancer (median age at cancer diagnosis: 45 (IQR: 40-53) compared to 52 (42-63) years, respectively). Figure 7.1 shows the distribution of age at breast cancer diagnosis by HIV status and ABC-DO study site. Overall, there were very small numbers of HIV-infected patients in age groups above 60 years. Therefore, a further 407 women aged over 60 years were excluded from this analysis, leaving a total of 1090 Black women from Namibia (N=268), South Africa (403), Uganda (300) and Zambia (119).

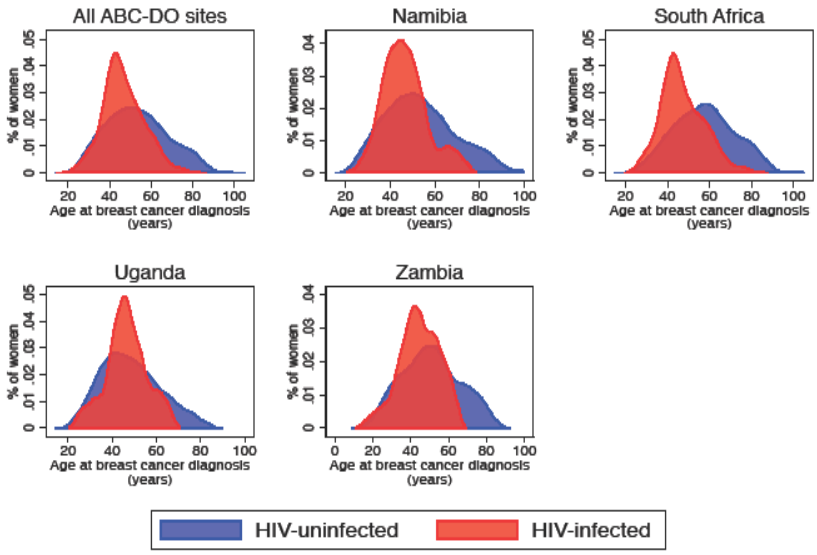

Figure 7.1 Age distribution of the ABC-DO women by HIV status, overall and by study site

Among the 1090 women included in this analysis, 284 (26%) were HIV-infected; 51 (19%) in Namibia, 146 (36%) in South Africa; 51 (17%) in Uganda; and 36 (30 % in Zambia) (appendix 2). As of 1 January 2019, a total of 413 (38%) women had died: 98 in Namibia, 122 in South Africa, 155 in Uganda, and 38 in Zambia. A total of 123 (43%) deaths occurred in HIV-infected patients vs. 290 (36%) in HIV-uninfected patients (Table 7.1). As expected, women with breast cancer in ABC-DO had higher mortality rates than women in the general population. The probability of dying in the next 3 years following breast cancer diagnosis (i.e., during follow-up) among ABC-DO women, regardless of their HIV status, was higher than the 3-year probability of death (from life tables) among HIV-infected and HIV-uninfected women in the general population across all ABC-DO participating countries (Figure 7.1). Furthermore, the probability of dying for women in the general population was only slightly higher among those who were HIV-infected compared to those who were HIV-uninfected consistent with differences in background mortality by HIV status being relatively small (Figure 7.2).

Table 7.1 Crude and net 1-year and 3-year survival by HIV status in the ABC-DO study, overall and by study site

		Namibia	South Africa	Uganda	Zambia	All sites
		(N=268)	(N=403)	(N=300)	(N=119)	(N=1090)
Statistic	**HIV status**					
No. women followed-up	HIV-	217	257	249	83	806
	HIV+	51	146	51	36	284
No. deaths at 3 years, n (%)	HIV-	76 (35.0))	69 (26.9)	128 (51.4)	17 (20.5)	290 (36.0)
	HIV+	22 (43.1)	53 (36.3)	27 (52.9)	21 (58.3)	123 (43.3)
Crude 1-year survival % (95% CI)	HIV-	87.0 (81.3-91.0)	90.7 (86.4-93.6)	72.7 (65.7-78.5)	83.4 (71.9-90.5)	83.7 (80.8-86.3)
	HIV+	82.6 (68.2-90.9)	84.2 (77.2-89.2)	76.5 (61.5-86.2)	59.8 (40.4-74.7)	79.5 (74.1-83.9)
Net 1-year survival % (95% CI)	HIV-	88.6 (83.7-93.5)	92.5 (88.9-96.2)	74.1 (67.6-80.6)	85.0 (75.8-94.1)	85.4 (82.7-88.2)
	HIV+	83.9 (72.9-95.0)	85.9 (79.8-91.9)	77.8 (65.6-90.0)	60.7 (43.4-77.9)	81.0 (76.1-86.0)
Crude 3-year survival % (95% CI)	HIV-	62.0 (54.8-68.4)	64.0 (55.8-71.1)	42.8 (36.1-49.3)	72.3 (58.7-82.1)	55.9 (51.8-59.8)
	HIV+	54.9 (40.0-67.6)	48.3 (35.2-60.3)	41.7 (27.2-55.5)	26.5 (11.3-44.6)	46.4 (39.2-53.3)
Net 3-year survival % (95% CI)	HIV-	65.9 (58.7-73.1)	68.3 (60.1-76.4)	45.4 (38.4-52.4)	76.7 (64.6-88.9)	59.5 (55.2-63.8)
	HIV+	58.1 (43.5-72.6)	51.3 (38.1-64.5)	44.2 (29.2-59.2)	27.9 (10.4-45.3)	49.2 (41.7-56.7)
Absolute crude 3-year survival difference between HIV+ and HIV- women (%)		7.1	15.7	1.1	45.8	9.5
Absolute net 3-year survival difference between HIV+ and HIV- women (%)		7.8	17	1.2	48.8	10.3

CI: confidence interval; HIV+: HIV-infected; HIV-: HIV-uninfected

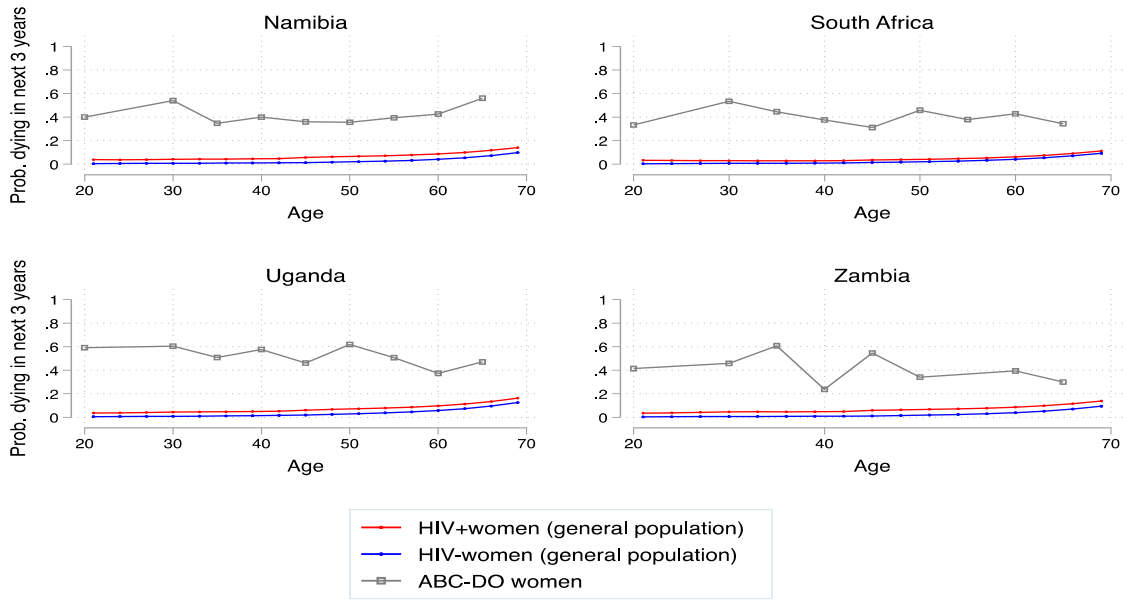

Figure 7.2 3-year probability of dying in the general femalr population by HIV status and probability of dying during 3-year follow-up among ABC-DO breast cancer women aged 60 years or below (regardless of HIV status)

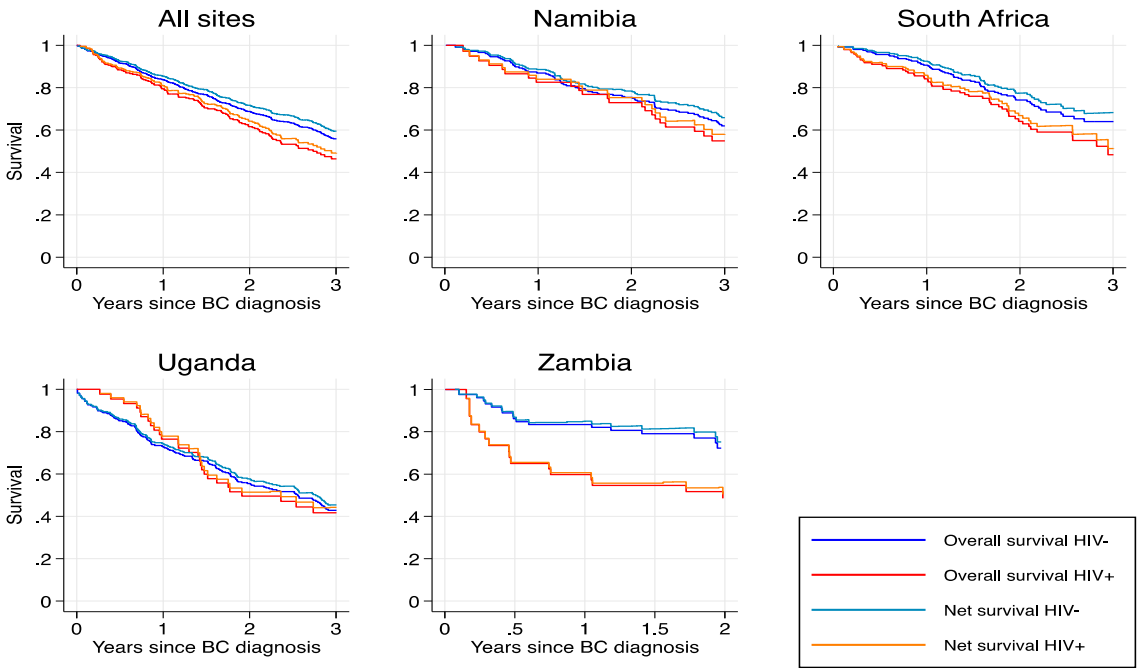

Figure 7.3 Kaplan Meier curves showing 3-year overall and net survival by HIV status for ABC-DO women aged 60 or below, overall and by study site

Figure 7.3 shows crude and net survival at 3 years following a breast cancer diagnosis, by HIV status, separately for each ABC-DO study site and for all sites combined. Both crude overall survival and net survival were lower among HIV-infected patients compared to HIV-uninfected patients for all study sites combined, but with variations across sites. The crude overall survival at 3 years for all sites combined was 46% (95% CI 39-53) in HIV-infected patients with breast cancer compared to 56% (52-60) in HIV-uninfected women. Three-year net survival was higher overall but remained 10% lower, in absolute terms, among HIV-infected patients (49% (42-57)) than their HIV-uninfected counterparts (59% (55-64)) for all sites combined. The absolute differences in net survival between HIV-infected and HIV-uninfected women varied across study sites, ranging from as low as 1% in Uganda to 8% in Namibia, 17% in South Africa and 49% in Zambia. However, there was not much difference between crude and net three-year survival estimates in the two groups of women i.e., net survival estimates increased by 1-3% among HIV-infected patients compared to 2-4% among HIV-uninfected patients, across sites (Table 7.1).

All-cause mortality hazard

The results of Cox regression showed that, overall, the hazard of all-cause mortality was higher for the HIV-infected patients, compared to the HIV-uninfected patients (crude HR 1.32 (1.07-1.63)), even after adjusting for age and stage at breast cancer diagnosis (adjusted HR 1.41 (1.13-1.75)). These results were consistent across all study sites albeit more pronounced in some sites than others. For example, the hazard of death was not statistically different between women with and without HIV in Namibia and Uganda (Table 7.2).

Excess hazard (accounting for background mortality by HIV)

For all sites combined, the crude excess hazard of death from any cause was 28% higher for the HIV-infected relative to HIV-uninfected breast cancer patients (excess HR 1.28 (1.02-1.63). This excess persisted after adjusting for age and stage at breast cancer diagnosis (adjusted excess HR 1.38 (1.09-1.76), slightly lower than the overall adjusted all-cause HR reported above (1.41 (1.13-1.75) (Table 7.2). This pattern was similar across study sites. Thus, the increased mortality in HIV-infected patients due to their higher background mortality was minimal.

Table 7.2 Crude and age-tumour stage-adjusted hazard ratios for 3-year all-cause mortality by HIV status, before and after controlling for HIV background mortality, in the ABC-DO study overall and by study site

		Namibia		South Africa		Uganda		Zambia		All sites	
Model	**HIV status**	**HR (95% CI)**	**Excess HR (95% CI)**	**HR (95% CI)**	**Excess HR (95% CI)**	**HR (95% CI)**	**Excess HR (95% CI)**	**HR (95% CI)**	**Excess HR (95% CI)**	**HR (95% CI)**	**Excess HR (95% CI)**
Crude	HIV-	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	HIV+	1.26	1.17	1.48	1.47	1.12	1.07	3.00	3.05	1.32	1·28
		(0.79-2.03)	(0·68-2.03)	(1.04-2.12)	(0.99-2.17)	(0.74-1.69)	(0·68-1.70)	(1.58-5.96)	(1.53-6.08)	(1.07-1.63)	(1·02-1·63)
+ Age *	HIV-	1.00	1·00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	HIV+	1.29	1·20	1.53	1.51	1.14	1.10	2.92	2.96	1.35	1·32
		(0.80-2.10)	(0.69-2.10)	(1.06-2.21)	(1.01-2.27)	(0.75-1.75)	(069-1.76)	(1.54-5.56)	(1.48-591)	(1.09-1.67)	(1·04-1·67)
+ Tumour stage *	HIV-	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	HIV+	1.62	1.44	1.59	1.60	1.07	1·03	3.10	3.10	1.41	1·38
		(0.99-2.65)	(0.80-2.59)	(1.10-2.31)	(1.06-2.41)	(0.70-1.65)	(0.64-1.66)	(1.60-6.02)	(1.51-6.36)	(1.13-1.75)	(1·09-1·76)

CI: confidence interval; HIV+: HIV-infected; HIV-: HIV-uninfected; HR: hazard ratio.
* At breast cancer diagnosis

Discussion

As more HIV-infected women survive into older ages, breast cancer will increasingly become an important cause of morbidity and mortality[2,26,27]. Consistent with other studies[6,10,28], we previously reported that HIV-infected breast cancer patients in SSA had lower overall survival than HIV-uninfected breast cancer patients even after adjusting for relevant patient and tumour prognostic factors[5,7]. The lower overall survival in HIV-infected patients may be due to (i) increased breast cancer-specific mortality, (ii) increased non-breast cancer related mortality in patients with both HIV and breast cancer compared with HIV-uninfected counterparts; or (iii) higher background mortality rates than among HIV-uninfected women due to AIDS-related and other causes of death[11]. In the present study, we estimated three-year relative survival rates of breast cancer in HIV-infected and HIV-uninfected women. Across all study sites, we found that HIV-infected patients still experienced excess mortality than their HIV-uninfected counterparts even after accounting for differences in background mortality between the two groups. There was only a slight difference between overall and relative survival estimates. Thus, our findings suggest that the contribution of higher background mortality associated with HIV to the increased mortality in HIV-infected breast cancer patients is minimal in SSA.

Our findings are consistent with reports from studies in the US. Coghill et al. compared all-cause mortality rates in HIV-infected patients with breast cancer to HIV-uninfected patients with breast cancer, HIV-infected patients without cancer and individuals with neither HIV nor cancer. They found that among non-white women aged under 70 years, HIV-infected women still had excess mortality even after accounting for effects of background mortality, HIV-associated mortality and breast cancer-associated mortality[12]. Another US study analysing cause-specific survival, using cancer registry-Medicare linked data, found that the breast cancer-specific mortality in HIV-infected patients was nearly two times (HR 1.85 (0.96-3.55)) higher than that of HIV-uninfected patients[13]. In another study of cancer patients linked to HIV/AIDS registries, Coghill et al. reported that HIV-infected patients still experienced 2.6 times (1.86-1.44) higher breast cancer-specific mortality than did women without HIV even after adjusting for cancer treatment[15].

In our study, relative survival for breast cancer was 10% lower for HIV-infected patients compared to HIV-uninfected patients. However, we found only a very slight difference between overall and net survival across all study sites. HIV-infected patients still experienced excess mortality even after adjusting for differences in background mortality between women with and without HIV, that is, differences in HIV-associated background mortality contributed very little to the excess mortality in HIV-infected patients. However, limitations in the methods

used to estimate the background mortality rates may account for these findings. The life tables used in this study were constructed based on UNAIDS HIV mortality estimates. Due to lack of viable civil registration and vital statistics in most SSA countries, the UNAIDS through Spectrum tool[23], models mortality based on HIV prevalence results from sentinel surveillance programs (predominantly surveillance of pregnant women attending antenatal care clinics) and from nationally-representative population-based surveys and other mortality data sources, in countries with generalised epidemics such as in SSA. However, data from nationwide surveys in most countries with generalised epidemics are not conducted frequently leaving antenatal clinic surveillance as a main source for informing national prevalence trends. Thus, a major assumption underlying the construction of the lifetables used this study is that data from antenatal clinics could be used to estimate adult HIV prevalence and model AIDS mortality in the general population[29]. This might lead to biased estimates if these clinics are not representative of all adult women. Mortality estimates derived from these data will most likely be reliable in younger age groups (< 35 years) whilst the current peak age at breast cancer diagnosis of HIV-infected patients in SSA is at 35-49[2]. Additionally, when modelling mortality estimates, the Spectrum model relies on mortality data from patients receiving ART captured by the International Epidemiology Databases to Evaluate AIDS (IeDEA) Collaboration[30]. In the current Spectrum model, the mortality rates for women on and off ART have gaps at ages 34-44 and 45-54 (appendix 3) due to changing age groups against which the mortality data are applied. These are the same age groups to which most of women in the ABC-DO study belong. The sudden variations in mortality rates are unlikely to be real. Future similar cancer survival studies will benefit from smoothing of background mortality rates in HIV-uninfected and HIV-infected populations and extending to older age groups.

On the other hand, our finding that the lower overall survival for HIV-infected breast cancer patients relative to their HIV-uninfected counterparts was not primarily driven by high background mortality associated with HIV, may hold true, particularly in SSA, if improvements in access to potent ART that have led to remarkable reductions in HIV/AIDS mortality[31,32], mean that HIV-infected patients now have similar risk of all-cause mortality as the general population[33-36] i.e., the excess death due to HIV/AIDS are being prevented by ART.

The reasons for the observed poorer relative survival in HIV-infected breast cancer women remain unclear. Prior studies have consistently shown that breast tumours in women with HIV are not biologically distinct. Women with HIV, at least in SSA, are as more likely to present with advanced-stage disease as do HIV-uninfected women[26]. There has been little

suggestion as to whether tumour receptor subtypes differ by HIV status[5,37-39]. Potentially, pathways leading to these survival disparities may be due to higher breast cancer-specific mortality rates in HIV-infected women compared to HIV-uninfected women because of differential access, management, and treatment between women with and without HIV. Women with HIV may receive inadequate treatment due to difficulties in accessing care or modified regimens and may also experience enhanced side effects of ART and cancer drug-to-drug interactions leading to intensified treatment-related toxicities and adverse outcomes. However, we lacked HIV treatment data, and their toxicities, which could have shed light on treatment interactions and their implications on survival. Additionally, HIV-infected breast cancer patients may also experience higher non-breast cancer-related mortality than women in the general population, including women with HIV only, because of psychological distress due to intersectional stigma, suicide and challenges with adherence to HIV treatment whilst on cancer therapy[11]. There may also be other underlying biological mechanisms such as the role of immunosuppression in enhancing aggressiveness of the cancer or compromising treatment efficacy[12], which we could not explore as data on HIV-related factors (CD4 T-cell count, viral load etc.) were largely missing.

In summary, our study has several strengths including its prospective nature, large size, substantial proportion of women with HIV, availability of detailed clinical and epidemiological data, and minimal losses to follow-up[40]. In addition, we were able to generate and use, for the first time in SSA, HIV-specific national life tables to obtain the expected rates of death by HIV status and estimate relative survival. Our findings show that women with HIV in the ABC-DO study experienced excess mortality at 3 years post-diagnosis than did their HIV-negative counterparts, even after taking into account differences in HIV-associated background mortality between the two groups. More studies are needed to evaluate and adjust for the influence of treatment, treatment-related toxicities, and HIV-related factors. This will require collection of more granular data on both HIV and breast cancer to uncover the underlying reasons for the excess mortality in this unique patient population.

Acknowledgements

We thank all the women who participated in this study, their families and all interviewers and hospital staff involved in this study.

Data availability ABC-DO study data are available and can be accessed at the International Agency for Research on Cancer through collaborative work. Requests should be made to env@iarc.fr.

Disclaimer

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

Funding information

ABC-DO Study received funding from Susan G Komen (grants IIR13264158, GSP18IARC001, and GSP19IARC001), the National Cancer Institute (grant R01CA244559), and the International Agency for Research on Cancer Branch of Environmental and Lifestyle Epidemiology. SABCHO was supported by R01CA250012. This paper is part of work undertaken for a PhD for SC, supported by the UK-Commonwealth Scholarship

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Chapter 8 Discussion

8.1 Introduction

This thesis investigated the role of HIV status on the patient journey (presentation, diagnosis, and survival) of women diagnosed with breast cancer in sub-Saharan Africa (SSA) using data from the multi-country hospital-based ABC-DO prospective cohort study. In this chapter, I provide a summary of key thesis findings and highlight their strengths and limitations. I also provide a framework for future research by highlighting epidemiological considerations that researchers should consider when investigating the extent and reasons for breast cancer survival disparities between HIV-infected and HIV-uninfected women, particularly in SSA. The proposed framework is presented as a research paper (commentary) published in the ASCO Journal of Global Oncology on 19 April 2023.

8.2 Summary of key findings

8.2.1 Research objective 1: *To assess the validity of self-reported HIV-status information, and identify predictors of accurate self-reporting of an HIV-positive status in Sub-Saharan Africa*

In chapter 4, I used data from the Karonga HDSS to assess the validity of self-reported HIV status with a focus on accuracy of and factors that may influence accurate self-reporting a HIV-positive status. In this study, information on HIV test results were linked to subsequent self-reported HIV status, and calculated sensitivity, specificity, positive- and negative predictive values for self-reported HIV status. I found very high sensitivity (86.4%, 95% CI: 84.8 – 88.0) and specificity (99.8, 95% CI: 99.7 – 99.9) for self-reported HIV status. Positive- and negative predictive values for self-reported HIV status were 98.1% (95% CI: 97.3 – 98.7) and 98.3% (98.1 – 98.5) respectively. Higher sensitivity and positive predictive value were observed in older age groups (sensitivity = 91.1% in those aged 45+ years vs. 65.5% in 15-24 year olds), among those who were married (84.8% in those currently married vs. 75.6% in never married), those with shorter time interval between HIV testing and self-reported HIV status interview (94.3% in individuals self-reporting HIV status within 6 months vs. 76.1% in those reporting after 2-4 years). Also, individuals who self-reported their HIV status in clinical settings had higher sensitivity and positive predictive value than those interviewed in community settings.

In multivariable analyses of predictors of accurate self-reported HIV-positive status, individuals who were younger were less likely to accurately report their HIV-positive status

than older adults. Adjusted prevalence ratios (PR) were 0.71 (95% CI: 0.61 – 0.83) among 15-24 years olds and 0.87 (0.83 – 0.91) in 25-34 age groups vs. the baseline 45+ years age group. Reassuringly for this thesis, individuals interviewed in clinical settings were more likely to accurately self-report their HIV-positive status than counterparts interviewed in community settings (adjusted PR, 1.07 (1.02 – 1.11).

8.2.2 Research objective 2: *To examine differences in patient's journey to breast cancer diagnosis and breast tumour characteristics at diagnosis, by HIV status*

In chapter 5, I examined the pre-diagnostic interval for breast cancer diagnosis in SSA and whether its length differs between HIV-infected and HIV-uninfected women diagnosed with breast cancer. I used data from the ABC-DO study in which detailed self-reported information was collected on the pre-diagnostic experience including dates when women first noticed their breast cancer symptoms, made first contact with both informal and formal healthcare providers. Among 1035 (152 were HIV-infected) women included in this study, I found no association between HIV status and tumour characteristics such as stage at diagnosis – a key prognostic factor for breast cancer. The proportion of HIV-infected women diagnosed with advanced-stage breast cancer was as high as among HIV-uninfected women in all countries combines (59.9% vs. 60.1% respectively) and for each country individually. HIV-infected women were younger at breast cancer diagnosis (mean age = 46 years (SD: 10)) compared with HIV-uninfected women (51 years (15)).

The median length of the total pre-diagnostic interval (i.e., from date of first symptom recognition to date of definitive diagnosis) was 8.4 months (IQR, 3.8 – 19.3) overall and did not significantly differ between HIV-infected (8.1 months, IQR: 4.1 – 19.4) and HIV-uninfected women (8.3, 3.5 – 19.1) for all sites combined. However, across participating countries, HIV-infected women in Uganda had slightly shorter interval than did HIV-uninfected women (9.2, 5.3 – 19.4 vs. 11.1, 5.6 – 22.9 respectively) while in Zambia HIV-infected women had slightly longer interval compared with HIV-uninfected women (9.2, 5.9 – 27.2 vs. 7.1, 2.6 – 25.9 respectively).

There was no evidence for an association between length of the pre-diagnostic interval and HIV status even after adjusting for relevant patient and breast cancer awareness factors (adjusted IRR 1.06, 95%CI: 0.89 – 1.28). Only country and level of education were associated with length of pre-diagnostic interval. Relative to Namibian women, women in Uganda were associated with 38% increased risk of a longer pre-diagnostic interval (adjusted IRR 1.38, 1.17 – 1.63). Women who were least educated (none/primary education)

had 40% increased risk of a longer pre-diagnostic interval than did women with secondary or higher education (adjusted IRR 1.40, 1.19 – 1.65).

8.2.3 Research objective 3: *To examine differences in overall survival after a breast cancer diagnosis by HIV, and their determinants.*

In chapter 6, I used data from the ABC-DO study to estimate overall survival following a breast cancer diagnosis in HIV-infected women compared with HIV-uninfected women. I also investigated associations between HIV status and patient/tumour characteristics to identify determinants of survival disparities between the two groups of breast cancer patients.

HIV-infected women were younger at cancer diagnosis and had lower BMI than HIV-uninfected women. There was no evidence for differences between HIV-infected and HIV-uninfected women in terms of their tumour stage, grade, and receptor subtypes. Three-year overall survival after a breast cancer diagnosis was poorer in HIV-infected women (46%, 95% CI: 40 – 54) compared with HIV-uninfected women (55%, 52 – 59). HIV-infected women were associated with 41% increased risk of all-cause mortality after a breast cancer diagnosis compared with HIV-uninfected women with breast cancer (adjusted HR 1.41, 95% CI: 1.15 – 1.74). Stage at diagnosis was a key determinant of survival disparities between HIV-infected and HIV-uninfected women. HIV-infected women had increased risk of mortality than HIV-uninfected women of the same stage of disease, with the HIV survival differential being stronger in women with non-metastatic disease (TNM stage I-III). Among the latter, HIV-infected women had a 65% increased risk of all-cause death relative to their HIV-uninfected counterparts (adjusted HR 1.65, 1.30 – 2.10). Women with metastatic disease had low survival regardless of HIV status.

8.2.4 Research objective 4: *To examine relative (net) survival after a diagnosis of breast cancer in HIV-infected women relative to their HIV-uninfected women with breast cancer.*

In addition to ABC-DO study data, in this chapter I used UNAIDS mortality data to generate HIV-specific life tables which were used to estimate relative (net) survival in HIV-infected breast cancer patients compared with HIV-uninfected breast cancer patients. This was done to take into account the differences in background mortality between the two groups of patients given than HIV-infected women may have higher background mortality due to increased risk of both HIV/AIDS-related mortality and non-breast cancer deaths.

In this study, I found that relative (net) survival was lower in HIV-infected women compared with HIV-uninfected women with breast cancer. However, there was only a slight difference between overall and net survival suggesting that the observed survival disparities between

HIV-infected and HIV-uninfected women with breast cancer was not primarily driven by differences in background mortality between the two groups.

8.3 Strengths and limitations of this thesis

In each of the previous chapters, where applicable, I discussed the strengths and limitations of data sources and methodological approaches used in each study. This chapter reiterates key strengths and limitations in the context of the thesis as a whole.

8.3.1 Large sample size spanning across different SSA settings

As noted in previous chapters, many of published studies investigating the role of HIV status on breast cancer in SSA are often limited in their sample size. The ABC-DO study is one of largest breast cancer cohorts in SSA, including a relatively high number (over 300) of HIV-infected women. The study was implemented in five African countries with varying HIV prevalence, diverse catchment populations, breast cancer incidence and healthcare systems. Detailed clinical and epidemiological data were collected on the entire patient's journey from symptoms to diagnosis and survival. This enabled a comprehensive examination of the role of HIV on the whole breast cancer spectrum.

8.3.2 Use of mHealth technology

The ABC-DO study was implemented using mHeath technology for study management, data collection and quality control. This meant that a common protocol could easily be used/implemented across study sites/countries, thus ensuring the collection of standardised high-quality data. More importantly, the technology was also used in active follow-up of patients. This included automated real-time reminders to staff when a follow-up was due. As a result, the ABC-DO study boasts of very low rates losses-to-follow-up and timely notification of deaths[1].

8.3.3 Prospectively collected data

The thesis benefits from the fact that data used in the studies presented therein were from sources that collected the data prospectively with relatively longer duration of follow-up periods. For example, the data from Karonga HDSS was collected prospectively for over 10 years. The ABC-DO study prospectively collected data and followed-up patients for a minimum of three years. Thus, the exposure (HIV status in this case) is unlikely to be misclassified because of recall bias or observer bias. Similarly, the findings presented in this thesis are not biased by knowledge of outcomes status as the outcome had not occurred yet at the time of enrolment (except lengths of pre-diagnostic intervals in chapter 5).

8.3.4 Generalizability

This thesis used multiple sources of data. Firstly, the Karonga HDDS is a population-based surveillance program in rural northern Malawi, a country which is not part of the ABC-DO study. This may affect the generalisability of reported findings on accuracy and validity of self-reported HIV status. However, being a country within the same region, with similar HIV prevalence, economic and health profile, and the high proportion of HIV-infected individuals who now know their HIV-status, the results from this study can to some extent be extrapolated to ABC-DO study sites.

The ABC-DO study was a hospital-based cohort. The study population used in this thesis may not be representative of all breast cancer patients in SSA. Some breast cancer patients who may not seek care or be referred are likely to have been missed, and if they were somehow different to those that sought care, then bias might have occurred. However, ABC-DO participating hospitals were all tertiary centres, which often were the only cancer treatment centre in the participating country. Also, ABC-DO study participation was very high (99%). Thus, selection bias may be minimal.

8.3.5 Misclassification of HIV status

HIV status was the main exposure under study in this thesis. It was ascertained through woman self-reported HIV status in most of the ABC-DO study sites. ABC-DO study being a general breast cancer cohort, HIV testing was not part of the protocol. Therefore, there is a risk of a non-differential exposure misclassification which may lead to underestimation of the effect of HIV status on outcomes. However, there was a high proportion (>50%) of women with tested HIV status in South Africa (where HIV testing was done). Additionally, self-reported HIV status was obtained at two distinct timepoints, at baseline interview and at presenting symptoms questionnaire. I found a high level of within-woman agreement of HIV-self reports taken at the two different time points. The overall consistency of findings across different countries also indicates that misclassification of self-reported HIV status was probably minimal. I also conducted sensitivity analyses in which women with unknown HIV status were classified as being either HIV-positive or HIV-negative and the results showed that any potential exposure misclassification would have had little effect the findings.

8.4 Research implication and direction for future research

8.4.1 Research paper 4

Survival disparities between patients with breast cancer with and without HIV: A research framework

https://ascopubs.org/doi/full/10.1200/GO.22.00330

RESEARCH PAPER COVER SHEET

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Student ID Number	LSH396778	**Title**	Mr.
First Name(s)	Steady Jerome Dickson		
Surname/Family Name	Chasimpha		
Thesis Title	Breast cancer in women living with HIV in Sub-Saharan Africa: presentation, diagnosis, and survival		
Primary Supervisor	Prof. Isabel dos-Santos-Silva		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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When was the work published?	19 April 2023		
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BREAST CANCER

commentaries

Survival Disparities Between Patients with Breast Cancer With and Without HIV: A Research Framework

Steady Chasimpha, MSc[1]; Isabel dos Santos Silva, PhD[1]; Yehoda M. Martei, MD, MSCE[2]; Surbhi Grover, MD, MPH[3]; Herbert Cubasch, MD[4,5]; and Valerie McCormack, PhD[6]

Introduction

Because of potent antiretroviral therapy (ART), most women infected with HIV now live longer to ages when breast cancer incidence rates are high.[1] Although not at increased risk of breast cancer, patients with HIV and breast cancer experience lower survival compared with their HIV-uninfected counterparts. A large US cancer- and HIV-linked registry-based study of patients with cancer, the HIV/AIDS-Cancer Match study, showed that all-cause mortality and breast cancer–specific mortality were 4.6 times (hazard ratio [HR]; 95% CI, 3.9 to 5.5) and 2.6 times (2.1-3.3), respectively, higher among patients with HIV and breast cancer (n = 314) than among patients with breast cancer uninfected by HIV, after adjusting for ethnicity and age, year of diagnosis, and tumor stage at cancer diagnosis.[2] Similarly, in Sub-Saharan Africa (SSA) where breast cancer survival is on average lower than that in high-income countries,[3-5] we found that patients with breast cancer and HIV experience lower overall survival than patients with breast cancer uninfected by HIV. The absolute 3-year overall survival was 9% lower for patients with HIV and breast cancer (HR, 46%; 95% CI, 40 to 53) versus (HR, 55%; 95% CI, 52 to 59) for patients with breast cancer uninfected by HIV in the African Breast Cancer-Disparities in Outcomes (ABC-DO) study.[5,6] The ABC-DO study and South African Breast Cancer and HIV Outcomes (SABCHO) study,[7] to our knowledge, the two largest prospective cohorts of women newly diagnosed with breast cancer in SSA (n = 313 and 600 patients with HIV, respectively, with a small number contributing to both cohorts) reported age- and stage-adjusted all-cause mortality HRs in HIV-infected versus HIV-uninfected patients with breast cancer of 1.41 (95% CI, 1.15 to 1.74)[6] and 1.50 (95% CI, 1.22 to 1.85),[8] respectively.

The direct/indirect impacts of the convergence of HIV and breast cancer on the management and outcomes of these two diseases are under-researched, and the underlying mechanisms for these cancer survival disparities by HIV status remain unclear. Existing research has been limited to either studies too small and underpowered to examine contributory factors or to studies that are large but lack the granularity needed to properly investigate these survival determinants.

We propose a research framework to highlight epidemiologic considerations that researchers might consider when investigating the extent of, and reasons for, breast cancer survival disparities by HIV status, especially in SSA where most patients with HIV reside. The framework may be modified to reflect context-specific issues in other settings. We hope that it will provide a foundation for harmonized research to address critical knowledge gaps in HIV-associated survival disparities among patients with breast cancer.

Mortality Outcomes

Higher all-cause mortality rates in HIV-infected versus HIV-uninfected patients with breast cancer can be apportioned to different causes of deaths (Fig 1). First, patients with HIV and breast cancer might have higher rates of breast cancer–specific mortality than patients with breast cancer uninfected by HIV (Box C). Second, patients with HIV and breast cancer might have higher breast cancer–unrelated mortality than their HIV-uninfected counterparts (Box A + B), that is, because of deaths from AIDS and other non–breast cancer causes. These deaths include the higher background mortality rate of HIV-infected women than that of the female general population (Box A) and, possibly, rates of excess background mortality (Box B). Thus, the outcome definition is critical here and will affect the interpretation of findings, be it all-cause mortality, breast cancer–specific mortality, or other-cause mortalities. In the United States, analyzing all-cause mortality, Coghill et al[9] found excess mortality rates among patients with HIV and breast cancer who were non-White and under age 70 years, that is, an excess above that of the combined effects of background mortality, mortality associated with HIV and with having breast cancer. Because drivers of mortality differences include not only biologic but also setting-specific factors, similar work in other settings is warranted.

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on February 7, 2023 and published at ascopubs.org/journal/go on April 19, 2023: DOI https://doi.org/10.1200/GO.22.00330

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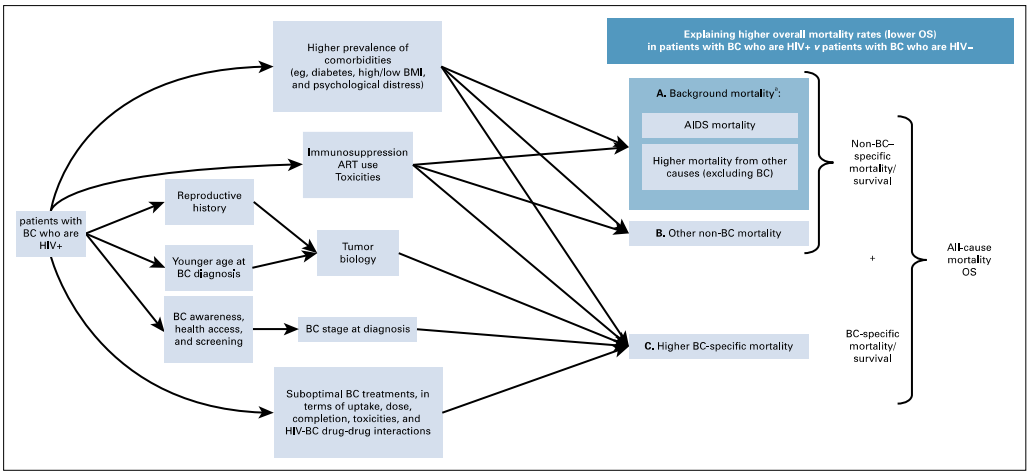

FIG 1. Potential pathways leading to higher overall mortality rates (lower OS) in patients with HIV and breast cancer. [a]Taken into account through net survival. ART, antiretroviral therapy; BC, breast cancer; OS, overall survival.

Higher breast cancer–specific mortality in HIV-infected versus HIV-uninfected patients with breast cancer (Box C) may occur for multiple reasons, including if patients with HIV (1) have less favorable breast tumor characteristics at diagnosis or (2) have poorer access or adherence to standard cancer-directed treatment or suffer intensified adverse effects and HIV-cancer drug-to-drug interactions (these pathways are expanded on below). Indeed, findings from US studies with information on cause of death reported that patients with HIV and breast cancer had higher breast cancer–specific mortality compared with their HIV-uninfected counterparts (adjusted HR ranging from 1.85 to 2.84[2,10,11]). Equivalent data are not available from SSA because of low-quality data on the cause of death.

The lower overall survival in HIV-infected versus HIV-uninfected patients with breast cancer may be partially because patients with HIV have higher background mortality than their HIV-uninfected counterparts in the general population, because of AIDS deaths or higher non-AIDS mortality (eg, because of higher prevalence of comorbidities such as diabetes or high/low BMI; Box A). Even in this era of ART, life expectancy in patients with HIV (with and without breast cancer) remains lower than that of the general population.[12-15] In addition, the copresence of HIV and breast cancer may lead to even higher non–breast cancer mortality (eg, because of psychological distress, suicide, and challenges of adherence to HIV treatment amid cancer therapy) than in the population of women with HIV only (Box B).

Differences in overall survival between HIV-infected versus HIV-uninfected patients with breast cancer use the all-cause mortality outcome (Box A + B + C to give $HR_{overall}$). If net/relative survival methods are used, they examine all-cause mortality, adjusted for background mortality, by accounting for deaths that would have occurred over the follow-up period in a similar age- and HIV-specific population of women without breast cancer (ie, removing differences because of Box A, giving HR_{net}). These net/relative survival methods use lifetables as the source of background mortality. Construction of lifetables requires information on observed age- and sex-specific mortality rates from national civil registration and vital statistics (CRVS) systems. In SSA, CRVS are often inadequate (often concentrated on cities, recorded cause of death information may be inaccurate and registered deaths are often not medically certified[15,16]). As such, mortality statistics/lifetables for most countries in SSA are calculated largely using prediction models and estimation procedures. In addition, estimating relative survival in the present context requires HIV-specific lifetables. The United Nations Joint Programme on HIV/AIDS produces annually updated mortality rates for the HIV-infected population, which can be used to generate national HIV-specific lifetables. However, these are also modeled mortality estimates,[16] predominantly on the basis of data from surveillance of pregnant women (15-49 years old) attending sentinel antenatal clinics or Prevention of Mother to Child Transmission programs. Thus, they will be most reliable in younger age groups (<35 years), whereas in SSA, the current peak age at breast cancer diagnosis for patients infected with HIV ranges from 35 to 49 years.[17] HIV-associated differentials will be larger in overall survival than in net survival (ie, $HR_{overall} > HR_{net}$). Among HIV-infected and HIV-uninfected women separately, differences in overall and net survival will greatly depend on mean survival after breast cancer. Higher

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background mortality may be sizable relative to few deaths from breast cancer in a setting of high mean survival, but may be negligible in a setting of low mean survival (regardless of HIV status), as is typically the case in SSA.

Breast Tumor Characteristics

Age, tumor stage, and tumor molecular subtype at breast cancer diagnosis may contribute to breast cancer–specific mortality differences if they differ substantially by HIV status. Currently, patients with HIV are diagnosed with breast cancer at younger ages compared with patients uninfected with HIV (approximately 10 years younger)[18,19] because patients with HIV are younger than HIV-uninfected women in the general population. However, it remains unclear whether HIV predisposes patients with HIV to early onset of breast cancer, an issue that may be setting-specific, and although initial findings do not suggest a difference,[6,20-22] further data on whether breast cancer subtypes differ by HIV are needed. Nevertheless, it is well established that younger patients with breast cancer uninfected by HIV present with more aggressive tumor subtypes, leading to poor prognosis and high recurrence rates.[23,24] Previous studies in SSA have shown no differences in tumor molecular subtypes by HIV status,[6,21,22,25,26] but this evidence is insufficient as there is limited routine access to high-quality immunohistochemistry services in most SSA.

Disparities in tumor stage at diagnosis by HIV status may vary between settings if they primarily reflect differences in breast cancer awareness, screening uptake, and/or disparities in health access or other social determinants of health. In the United States, patients with HIV might have lower access to screening or may develop breast cancer at younger ages than those targeted by screening or might have a higher incidence of interval cancers.[27] Screening for breast cancer, either opportunistic or population-based, is rather limited in SSA. Studies in the United States suggest that patients with HIV are twice as likely to present with advanced-stage (TNM stage IV) breast cancer as women without HIV,[27,28] but no such differences have been observed in SSA.[29]

HIV-Cancer Treatment and Toxicities

Pathways leading to higher breast cancer–specific mortality in patients with HIV may additionally reflect potential differences in treatment by HIV status (Fig 1). Adequacy of multimodality cancer treatment, including relative dose intensity for systemic treatment, has been associated with survival outcomes in patients with breast cancer, especially those with early-stage disease treated with curative intent. Breast cancer treatment completion may be an important mediator of the association between HIV and breast cancer survival outcomes, but treatment data are often critically missing or only available as a dichotomous variable (eg, treated *v* untreated) in studies evaluating these associations.[11,21,22,30] Key variables in standardized data collection tools should include complete information on systemic treatment including granular details on doses administered and dates of chemotherapy, timing and adequacy of curative surgery and total dose, timing and frequency of radiotherapy, type of ART, and virologic outcomes. These data will help investigate the contributory effects of treatment and toxicity and are actionable for reducing disparities in mortality/survival outcomes that may arise because of HIV-related differences in quality-of-cancer care being delivered, its uptake, and adherence.

Patients with HIV and breast cancer may also experience adverse effects of ART and cancer drug-to-drug interactions (DDIs), and lack of access to granulocyte colony-stimulating factors might lead to intensified treatment-related toxicities and side effects compared with their HIV-uninfected counterparts. ART regimens/agents, such as zidovudine (AZT—which is associated with high incidence of side effects such as anemia and neutropenia[31,32]), may influence chemotherapy by enhancing toxicity.[33] In addition, chemotherapeutic agents and HIV drugs might have overlapping toxicities because of DDIs, affecting dosage in patients with HIV.[34,35] In the AIDS Malignancy Consortium, patients with solid or hematologic tumors treated with sunitinib and on ritonavir protease inhibitor (PI)–based therapy experienced increased toxicity, including higher rates of grade 3 neutropenia, diarrhea, mucositis, and fatigue, even with reduced doses of sunitinib than patients on non–ritonavir PI-based therapy.[36] There are limited data on chemotherapy or treatment, and related toxicities, to dissect the impact of chemotherapy and ART-induced DDIs on survival among patients with HIV and breast cancer.

Health System and Social Factors

In SSA, HIV is typically managed locally, whereas cancer is managed in oncology centers in cities. These differences may pose logistical challenges for the patients and make it difficult for clinicians to comanage the two conditions. Limited oncologic or surgical expertise, lack of access to standard treatment (eg, because of transport costs to oncology centers), and unavailability of some treatment modalities such as radiotherapy (two thirds of SSA lack radiotherapy services[37,38]) may lead to higher cost of care in patients with HIV and breast cancer.[10] The lack of universal health care in most SSA countries means that patients with HIV and breast cancer bear the costs of treatment for both diseases out-of-pocket, leading to delayed or incomplete/no treatment. Indeed, studies have shown lower relative dose intensity of chemotherapy in patients with HIV and breast cancer,[39] which may lead to suboptimal therapy and potentially treatment failure and drug resistance.[35] In addition, there are many unanswered questions regarding the role of intersectional stigma and psychological distress in patients with HIV and breast cancer,[40] which may lead to their reduced adherence/abandonment of cancer treatment.

In conclusion, the anticipated increasing numbers of patients with HIV and breast cancer call for more research on reasons underlying survival disparities by HIV status. More funding is

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needed for large clinical cohorts of breast cancer (with and without HIV), with standardized collection of granular HIV-cancer treatment data, to fully understand treatment interactions and their implications on survival. Patients with HIV and breast cancer should be included in clinical trials, especially in settings with high numbers of patients with HIV and breast cancer (eg, South Africa [22%],[8] Namibia [15%], and Botswana [>20%][39,41]), to enhance external generalizability of efficacy and safety of cancer-directed therapy in these patients. Addressing these gaps will hopefully translate to evidence-based interventions for improved outcomes in patients with HIV and breast cancer.

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SUPPORT

This paper is part of the work undertaken for PhD research of Dr S.C. and was supported by the UK-Commonwealth Scholarships.

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Manuscript writing: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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Research Funding: Varian Medical Systems

No other potential conflicts of interest were reported.

JCO Global Oncol 9:e2200330. © 2023 by American Society of Clinical Oncology

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8.5 Conclusions

This thesis adds to existing research on the role of HIV status on the breast cancer patients' journey from presentation, diagnosis through to survival. In summary, I found that in SSA, HIV-infected women are as likely as HIV-uninfected women to have longer time intervals from when they first notice breast cancer symptoms to getting definitive breast cancer diagnosis, despite being already in regular contact with healthcare providers through ART care. Women in SSA were more likely to present with advanced-stage breast tumours regardless of their HIV status. Similarly, there was no evidence for associations between HIV status and other tumour characteristics such as tumour grade and receptor subtypes. Three-year overall survival was lower among HIV-infected women diagnosed with breast cancer compared with their HIV-uninfected women with breast cancer. The increased risk of all-cause mortality in HIV-infected women was greater than that of HIV-uninfected women of the same stage of disease, especially among women with non-metastatic breast cancer. HIV-infected women with breast cancer also had lower net survival than did HIV-uninfected with breast cancer. However, there was only a slight difference between overall and net survival suggesting that observed survival disparities between the two groups may not primarily be driven by differences in background mortality. To prevent deaths in this young patient group, further studies are needed, to determine whether the observed survival disparities reflect underlying biological mechanisms, differential access to and/or compliance to standard treatment or detrimental HIV-breast cancer treatment interactions and toxicities.

8.6 References

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Appendix A Supplementary information for chapter 4

Supplementary Table 4.1: Comparison of self-reporting of HIV status between the first and last set of HIV test result and subsequent self-reported HIV status among individuals who seroconverted.

	All (N=47)	
Change in self-reporting	N	%
Correct in both	26	55.3
Correct in first not last	20	42.6
Correct in last not first	0	0.0
Incorrect in both	1	2.1

Supplementary Table 4.2: Comparison of self-reporting of HIV status between the first and last set of HIV test result and subsequent self-reported HIV status (excluding individuals who seroconverted).

	HIV test result		
	Negative	**Positive**	**Total**
Change in self-reporting	**N (%)**	**N (%)**	**N (%)**
Correct in both	7564 (99.8)	375 (84.1)	7939 (98.8)
Correct in first not last	12 (0.2)	10 (2.2)	22 (0.3)
Correct in last not first	7 (0.09)	44 (9.9)	51 (0.7)
Incorrect in both	0 (0.0)	17 (3.8)	17 (0.2)
TOTAL	**7583 (100)**	**446 (100)**	**8029 (100)**

Appendix B Supplementary information for chapter 6

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Chasimpha S, McCormack V, Cubasc H, et al. Disparities in breast cancer survival between women with and without HIV across sub-Saharan Africa (ABC-DO): a prospective, cohort study. *Lancet HIV* 2022; **9:** e160–71.

Appendix

Supplementary List 1: List of ethics approval

1. IARC (IEC 13-19, IEC15-18)
2. LSHTM (6459, 16495)
3. Federal Medical Centre Owerri, Nigeria
4. Abia State University Teaching Hospital, Nigeria
5. University of Zambia Biomedical Research Ethics Committee (004-08-15), Zambia
6. University of Witwatersrand (M150345), Gauteng, South Africa
7. Uganda National Council for Science and Technology (HS 1588), Uganda
8. Ministry of Health and Social Services of Namibia (17/3/3)

Supplementary Table 1: **Information on previous studies and their published estimates on the effect of HIV on survival following a breast cancer diagnosis**

Author (Year)	Country (region)	Study design (study years)	Eligibility criteria	HIV exposure assessment	No. of HIV+ / HIV- BC women	Outcome(s)	HR for effect of HIV (95% CI)	Comments
Sub-Saharan Africa (SSA)								
Coghill et al (2013)(1)	Uganda	Retrospective cohort (population-based 2003-2010) – based on Kampala Cancer Registry Database and medical records at Uganda Cancer Institute and Mulago Hospital	Adults aged at least 18 years at diagnosis of common cancers including breast cancer	HIV ascertained based on documented positive HIV antibody test, medical history of HIV infection and an HIV clinic referral letter	24 / 196	All-cause mortality at 1 year following cancer diagnosis	(HR adjusted for age, year of cancer diagnosis and stage at diagnosis) 2·04 (0·76-5·47)	40% LTFU within 1 year of follow-up. Slightly better survival in more recent years- may be due to availability of ART or improvements in cancer diagnosis and treatment
Cubasch et al (2018)(2)	South Africa	Retrospective cohort (2009-2014)- based on ambient data at the Chris Baragwanath Academic Hospital (CHBAH)	Incident breast cancer women diagnosed at CHBAH	HIV testing was done	88 /411	All-cause mortality at 4 years following breast cancer diagnosis	(HR adjusted for age, stage, grade and receptor subtype) 1·39 (0·83-2·33)	48% LTFU at end of 4 years of follow-up Outcome (death of any cause) also included terminally-ill patients defined as patients unlikely to survive more than 3 months
Sadigh et al (2019)(3)	Botswana	Prospective cohort (2010-2018) based on data from the Thabatse Cancer Cohort – 4 oncology centres in Botswana	Women aged at least 18 years and with known HIV status	Not clearly specified	151 / 327	All-cause mortality at 5 years following breast cancer diagnosis	(HR adjusted for age, cancer stage, receptor subtype and income) 1·82 (1·32-2·49)	Conference abstract only Incomplete data on cancer stage, treatment and tumour receptor subtypes 1·5% LTFU at 5years
Brandao et al (2019)(4)	Mozambique	Prospective cohort (hospital-based -2015-2017)	Women diagnosed with breast cancer at Maputo Central Hospital	Not clearly specified	52 / 152	All-cause mortality within 2 years of follow-up	(Unadjusted HR) 1·52 (0·92-2·51)	Conference abstract only LTFU not reported
McCormack et al (2020)(5)	Namibia, South Africa, Zambia, Uganda and Nigeria	Prospective cohort (hospital-based 2014- to date)	Women aged at least 18 years with incident breast cancer	Self-reported HIV status	315 / 1841	All-cause mortality at 3 years following breast cancer diagnosis	(HR adjusted for age, stage and tumour grade) 1·48 (1·22-1·81)	Very low LFTU (5% Women with unknown HIV status were classified as being HIV-negative
North America								
Biggar et al (2005)(6)	USA (New York state)	Population-based cohort study (record linkage of cancer registry & HIV/AIDS registry records) (1980-2000)	Adults aged 15-69 yrs. at AIDS diagnosis and subsequently diagnosed with cancer	AIDS status as identified through linkage to the HIV/AIDS registry	67 / 15225	All-cause mortality within 2 years of the cancer diagnosis	(HRs adjusted for age, race, and calendar time of cancer onset) In 1990-1995: 5.4 (3.8-7.8); In 1996-2000: 1.6 (0.7-3.8)	Better survival in 1996-2000 when effective ART became available. The non-AIDS group included HIV+ individuals who never developed AIDS

Coghill et al (2015)(7)	USA (six states: Colorado, Connecticut, Georgia, Michigan, New Jersey and Texas)	Retrospective population-based cohort study – the HIV/AIDS Cancer Match study, a record linkage of several population-based registries (1996-2014)	Individuals diagnosed with 14 common invasive cancers during the HAART era (i.e. from 1996 to 2007-2010 depending on registry) with follow-up to the end of 2014	HIV status as identified through linkage to population-based HIV/AIDS registries	314 / 386041	(i) Cancer-specific mortality
						
						(ii) All-cause mortality
							(HRs adjusted for race and age, year and tumour stage at cancer diagnosis)
							
							For (i):
							All stages: 2·61 (2·06-3·31)
							Localised/regional: 2.61 (1.96, 3.41)
							
							For (ii):
							All stages: 4.62 (3.92-5.45)
							
							Localised/regional: NR
								From 1996 onwards both HIV and AIDS were reportable conditions in the USA.
								
								Further adjustment for receipt of any first-course treatment (i.e. surgery, chemotherapy, radiotherapy, hormonal therapy) did not affect the magnitude of the estimated HIV effect on breast cancer-specific survival.

Coghill et al (2019a)(8) Cancer	USA	National Cancer Database – nationwide hospital-based registry. Retrospective cohort based on the National Cancer Database, a nationwide hospital -based registry (2004-2014)	Patients diagnosed with selected cancer types, including female breast cancer, between 2004 and 2012, and followed-up to the end of 2014	HIV status clinically ascertained at the time of the cancer diagnosis.	Stages I-III only: 957 / 1,099,101 Stages I-IV: 1084 / 1,158,865	All-cause mortality	(HRs adj. for age, race, calendar year, household income, health insurance & cancer facility) <u>Stages I-III only:</u> 1·85 (1·68-2·04) Stages I-IV: 1.77 (1.62, 1.94)	HIV+ women had more advanced stage at BC diagnosis.
Coghill et al (2019b)(9) JAMA Oncol	USA	Retrospective population-based cohort assembled through record linkage of SEER and Medicare databases (1996-2014)	Patients aged ≥65 yrs. diagnosed with a single local or regional stage cancer who received appropriate treatment within the first year after cancer diagnosis and who survived at least 1 yr. after cancer diagnosis	HIV/AIDS diagnoses ascertained from Medicare claims	50 / 96124	(i) All-cause mortality (ii) Cancer-specific mortality	(HR adjusted for race, income, age, calendar year, stage at diagnosis and treatment) (i) 1.85 (0.96-3.55) (ii) 1·50 (1·01-2·24)	
Chhatre et al (2019)(10)	USA	Retrospective population-based cohort based on record linkage between SEER and Medicare databases (2003-2013)	Fee-for-service Medicare enrolees diagnosed with a primary breast cancer between 2000-2011 followed up to the end of 2013.	HIV/AIDS diagnoses ascertained from Medicare claims (physician, outpatient and inpatient claims)	176 / 163904	(i) All-cause mortality (ii) Breast cancer specific mortality	(HR adjusted for age, year at diagnosis, race, marital status, comorbidity, SE variables, tumour stage and treatment) (i) 2·99 (2·61-3·43) (ii) 2.84 (2.29, 3.52)	

ART: antiretroviral therapy; BC: breast cancer; CI: confidence internal; HR: hazard ratio; LTFU: losses to follow-up; NR: not reported; SE: socio-economic; SEER: Surveillance, Epidemiology, and End Results program.

Supplementary Table 2: **Hazard ratios for all-cause mortality at 3 years overall, conditional on being alive beyond 18 months in HIV+ vs. HIV- non-metastatic and metastatic breast cancer women in ABC-DO HIV subcohort**

	Crude HIV effect		Model A[α]		Model B[β]		Model C[γ]	
	Deaths/Total	**HR (95%CI)**	**Deaths/Total**	**HR (95%CI)**	**Deaths/Total**	**HR (95%CI)**	**Deaths/Total**	**HR (95%CI)**
All women								
HIV-	432/1184	1·00	432/1184	1·00	430/1179	1·00	232/717	1·00
HIV+	137/313	1·35 (1·11-1·63)	137/313	1·52 (1·24-1·87)	136/312	1·46 (1·19-1·79)	84/212	1·47 (1·12-1·93)
All women if alive beyond 18 months								
HIV-	163/821	1·00	163/821	1·00	163/818	1·00	91/513	1·00
HIV+	50/196	1·40 (1·02-1·93)	50/196	1·54 (1·10-2·16)	50/196	1·49 (1·06-2·10)	34/138	1·58 (1·03-2·44)
All non-metastatic women								
HIV-	285/965	1·00	285/965	1·00	284/961	1·00	149/606	1·00
HIV+	98/255	1·48 (1·18-1·87)	98/255	1·64 (1·29-2·09)	97/254	1·56 (1·22-1·99)	66/184	1·71 (1·25-2·34)
Non-metastatic women alive beyond 18 months								
HIV-	130/727	1·00	130/727	1·00	130/724	1·00	70/467	1·00
HIV+	41/172	1·49 (1·04-2·12)	41/172	1·58 (1·09-2·28)	41/172	1·52 (1·04-2·20)	29/127	1·66 (1·04-2·64)
All metastatic women								
HIV-	136/171	1·00	136/171	1·00	135/170	1·00	83/108	1·00
HIV+	28/39	0·95 (0·63-1·45)	28/39	1·10 (0·70-1·73)	28/39	1·07 (0·67-1·70)	18/28	0·98 (0·54-1·78)
Metastatic women alive beyond 18 months								
HIV-	31/62	1·00	31/62	1·00	31/62	1·00	21/44	1·00
HIV+	6/13	0·73 (0·30-1·78)	6/13	1·14 (0·42-3·11)	6/13	1·08 (0·35-3·40)	5/11	1·22 (0·32-4·63)

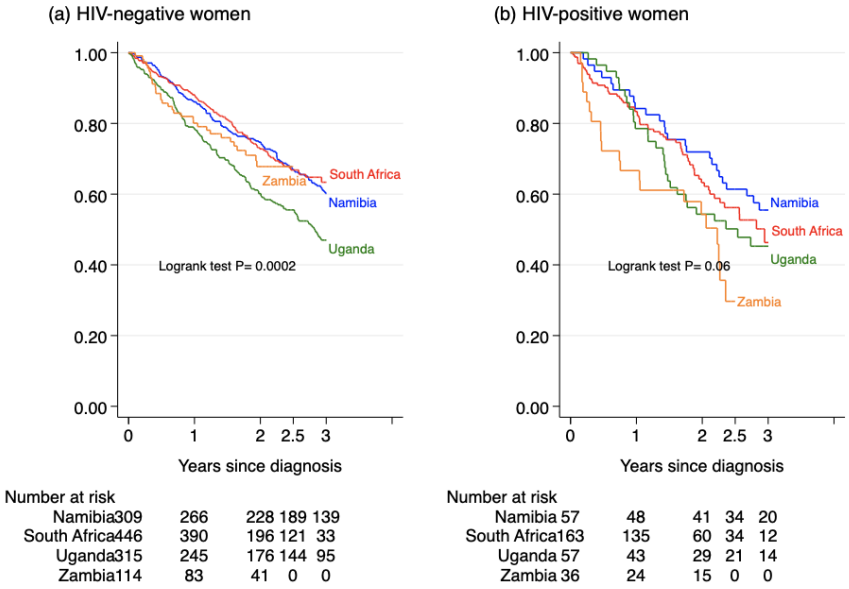
HR: hazard ratio; CI: confidence interval
α Model A: Cox regression model for HIV effect on all-cause model adjusted for age, stage and tumour grade at breast cancer diagnosis
β Mode B: Model A + others factors, namely socio economic position and formal education attained
γ Model C: Model B + tumour receptor subtype (HR+, HER2-; HR+, HER2+; HR-, HER2+; HR-,HER2-), available for Namibia and South Africa only

Supplementary Table 3: **Sensitivity analysis comparing adjusted HRs (stratified by country) for the association of HIV status with 3-year survival for summary stage (metastatic vs. non-metastatic) under different assumptions on HIV unknowns**

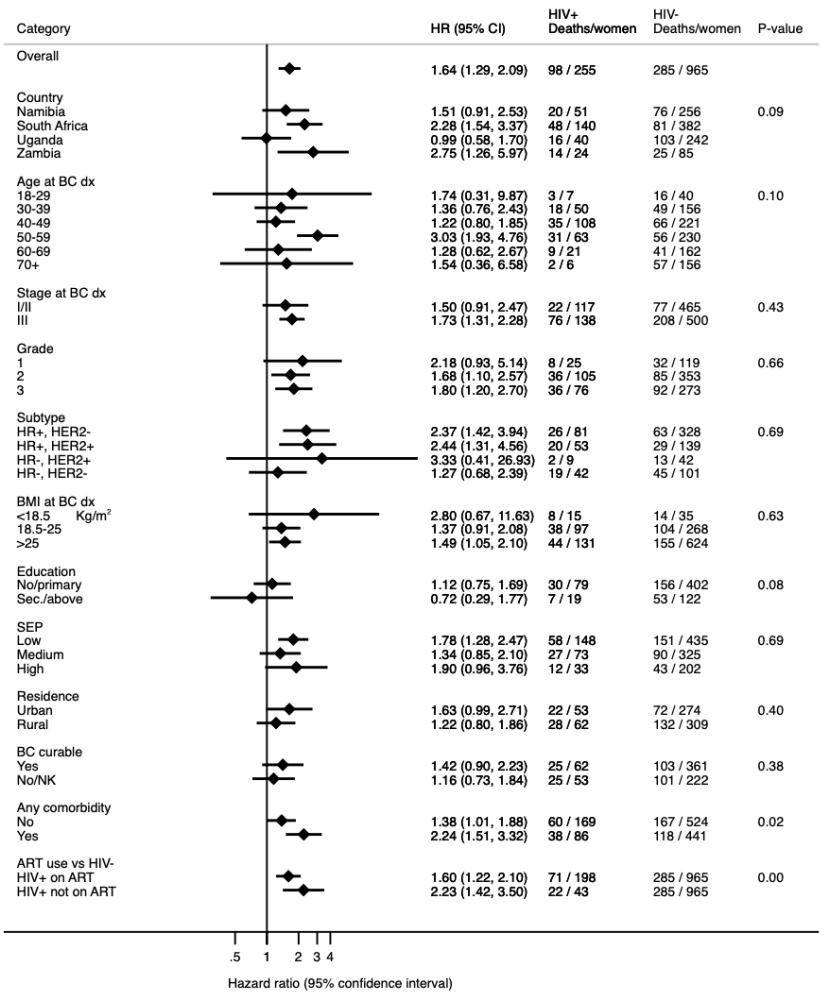
	All sites		**Namibia**		**South Africa**		**Uganda**		**Zambia[α]**
	Non-metastatic	**Metastatic**	**Non-metastatic**	**Metastatic**	**Non-metastatic**	**Metastatic**	**Non-metastatic**	**Metastatic**	**Non-metastatic**
ASSUMPTION	**HR (95% CI)[β]**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
HIV NK dropped									
HIV+ vs. HIV-	1·63	1·12	1·46	1·14	2·22	0·88	1·07	0·84	3·11
	(1·29-2·09)	(0·71-1·76)	(0·88-2·44)	(0·39-3·39)	(1·50-3·29)	(0·45-1·72)	(0·62-1·84)	(0·35-2·02)	(1·38-7·03)
HIV NK assumed HIV-positive									
HIV+ vs. HIV-	1·55	1·11	1·53	1·13	2·34	0·95	0·96	0·84	1·74
	(1·26-1·91)	(0·75-1·63)	(0·97-2·42)	(0·47-2·71)	(1·62-3·38)	(0·49-1·83)	(0·63-1·46)	(0·41-1·75)	(0·97-3·11)
HIV NK assumed to be negative									
HIV+ vs. HIV-	1·60	1·10	1·39	1·15	2·06	0·85	1·12	0·80	2·72
	(1·26-2·03)	(0·70-1·72)	(0·84-2·31)	(0·40-3·38)	(1·40-3·02)	(0·44-1·66)	(0·66-1·91)	(0·33-1·91)	(1·30-5·67)

α: There were only 10 deaths/13 total women with metastatic disease overall in Zambia, hence not included
β: Hazard ratio and 95% confidence interval adjusted for age and tumour grade at diagnosis
γ: HIV NK: HIV status not known

Supplementary Figure 1: **Kaplan Meier curves for 3-year overall survival from breast cancer by country and separately for (a) HIV-negative women and (b) HIV-positive women in the ABC-DO HIVsubcohort**

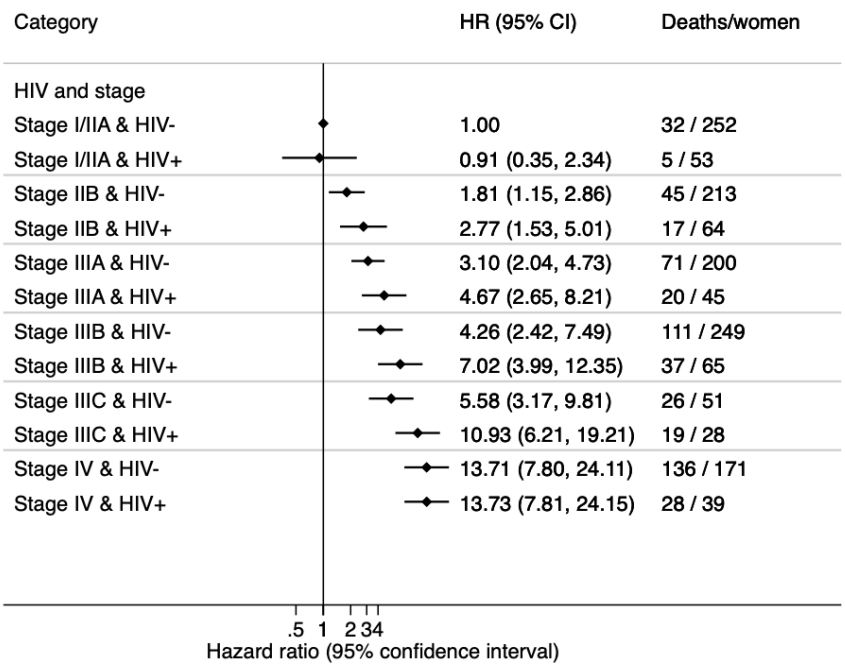


Supplementary Figure 2: **Hazard ratios for all-cause mortality in HIV+ vs HIV- women among non-metastatic patients at breast cancer diagnosis, by patient and tumour characteristic in the ABC-DO HIV subcohort**



Footnote:
ART: anti-retroviral therapy; BC: breast cancer; BMI: body mass index; CI: confidence interval; dx: diagnosis; HR: hazard ratio; NK: not known; Sec: secondary education; SEP: socio-economic position (see Table 1).
HR adjusted for age, tumour stage and tumour grade at breast cancer diagnosis.
P-value for interaction between HIV status and each patient and tumour variable listed.

Figure 1. **Hazard ratios for 3-year all-cause mortality stratified by HIV- status and tumour stage at breast cancer diagnosis in the ABC-DO cohort (all sites combined)**



Footnote:
CI: confidence interval; HR: hazard ratio
HRs adjusted for age and tumour grade at breast cancer diagnosis

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Appendix C Supplementary information for chapter 7

Appendix 1: List of ethics approvals

1. IARC (IEC 13-19, IEC15-18)
2. LSHTM (6459, 16495)
3. Federal Medical Centre Owerri, Nigeria
4. Abia State University Teaching Hospital, Nigeria
5. University of Zambia Biomedical Research Ethics Committee (004-08-15), Zambia
6. University of Witwatersrand (M150345), Gauteng, South Africa
7. Uganda National Council for Science and Technology (HS 1588), Uganda
8. Ministry of Health and Social Services of Namibia (17/3/3)

Supplementary Table 6.1 Patient (demographic and socio-economic) and tumour characteristics of ABC-DO women, by HIV status and country

	Namibia (n=268)		South Africa (n=403)		Uganda (n=300)		Zambia (n=199)		All sites (n=1090)	
	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-
Characteristic	N (%[α])	N (%[α])	N (%[α])	N (%[α])	N (%[α])	N (%[α])	N (%[α])	N (%[α])	N (%[α])	N (%[α])
Total (row %)	51 (19.0)	217 (81.0)	146 (36.2)	257 (63.8)	51 (17.0)	249 (83.0)	36 (30.3)	83 (69.7)	284 (26.1)	806 (73.9)
Age at BC diagnosis, years										
18-39	15 (29.4)	64 (29.5)	33 (22.6)	48 (18.7)	11 (21.6)	93 (37.4)	13 (36.1)	31 (37.4)	72 (25.4)	236 (29.3)
40-49	23 (45.1)	74 (34.1)	73 (50.0)	89 (34.6)	27 (52.9)	86 (34.5)	13 (36.1)	22 (26.5)	136 (47.9)	271 (33.6)
50+	13 (25.5)	79 (36.4)	40 (27.4)	120 (46.7)	13 (25.5)	70 (28.1)	10 (27.8)	30 (36.1)	76 (26.8)	299 (37.1)
		p^{β}=0.25		p=0.001		p=0.03		p=0.52		p<0.001
Education attained										
None/primary	21 (41.2)	79 (36.4)	16 (11.0)	40 (15.6)	28 (54.9)	129 (51.8)	15 (41.7)	38 (45.8)	80 (28.2)	286 (35.5)
Secondary/above	30 (58.8)	138 (63.6)	129 (88.4)	215 (83.7)	23 (45.1)	120 (48.2)	21 (58.3)	45 (54.2)	203 (71.5)	518 (64.3)
Missing			1 (0.6)	2 (0.7)					1 (0.3)	2 (0.2)
		p=0.53		p=0.20		p=0.69		p=0.68		p=0.03
Socio-economic position[δ]										
Low	29 (56.9)	78 (35.9)	103 (70.6)	126 (49.0)	27 (52.9)	145 (58.2)	13 (36.1)	25 (30.1)	172 (60.6)	374 (46.4)
Medium	17 (33.3)	85 (39.2)	30 (20.6)	87 (33.9)	13 (25.5)	53 (21.3)	13 (36.1)	31 (37.4)	73 (25.7)	256 (31.8)
High	5 (9.8)	54 (24.9)	12 (8.2)	42 (16.3)	11 (21.6)	51 (20.5)	10 (27.8)	27 (32.5)	38 (13.4)	174 (21.6)
Missing			1 (0.6)	2 (0.8)					1 (0.3)	2 (0.2)
		p=0.01		p<0.001		p=0.75		p=0.79		p<0.001
Area of residence										
Urban	30 (58.8)	143 (65.9)			14 (27.5)	77 (30.9)	25 (69.4)	55 (66.3)	69 (50.0	275 (50.1)
Rural	21 (41.2)	74 (34.1)			37 (72.5)	172 (69.1)	11 (30.6)	28 (33.7)	69 (50.0)	274 (49.9)

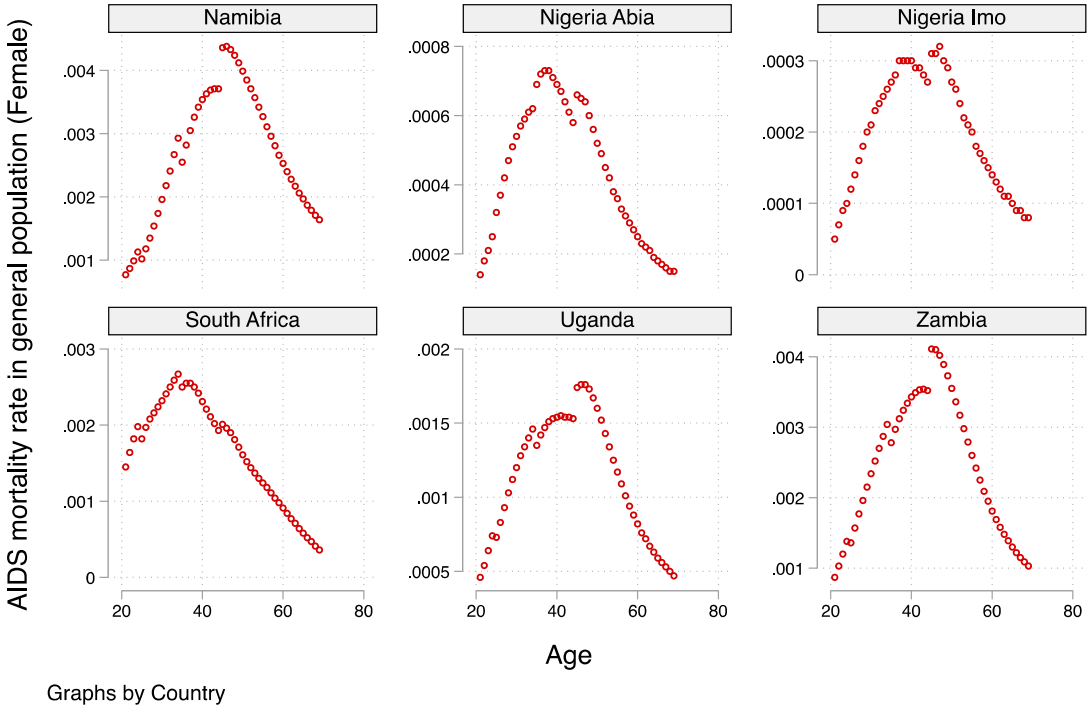
	Namibia (n=268)		South Africa (n=403)		Uganda (n=300)		Zambia (n=199)		All sites (n=1090)	
	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-
Characteristic	**N (%α)**	**N (%α)**	**N (%α)**	**N (%α)**	**N (%α)**	**N (%α)**	**N (%α)**	**N (%α)**	**N (%α)**	**N (%α)**
		p=0.34				p=0.62		p=0.73		p=0.99
Body Mass Index (Kg/m2)										
<18.5	6 (11.8)	15 (6.9)	7 (4.8)	3 (1.2)	0 (0)	12 (4.8)	4 (11.1)	2 (2.4)	17 (6.0)	32 (3.9))
18.5 - <25	21 (41.2)	71 (32.7)	53 (36.3)	29 (11.3)	26 (51.0)	107 (43.0)	17 (47.2)	32 (38.6)	117 (41.2)	239 (29.7)
25 - <30	16 (31.4)	63 (29.0)	31 (21.2)	49 (19.0)	14 (27.5)	38 (15.3)	10 (27.8)	24 (28.9)	71 (25.0)	223 (27.7)
30+	7 (13.7)	62 (28.6)	43 (29.5)	162 (63.0)	10 (19.6)	12 (4.8)	2 (5.6)	22 (26.5)	62 (21.8)	284 (35.2)
Missing	1 (1.9)	6 (2.8)	12 (8.2)	14 (5.5)	1 (1.9)	5 (2.0)	3 (8.3)	3 (3.6)	17 (6.0)	28 (3.5)
		p=0.13		p<0.001		p=0.23		p=0.02		p<0.001
Cohabiting										
No	38 (74.5)	134 (61.8)	110 (75.3)	157 (60.1)	34 (66.7)	118 (47.4)	19 (52.8)	27 (32.5)	201 (70.8)	436 (54.1)
Yes	13 (25.5)	83 (38.2)	36 (24.7)	100 (38.9)	17 (33.3)	131 (52.6)	17 (47.2)	56 (67.5)	83 (29.2)	370 (45.9)
		p=0.09		p=0.004		p=0.01		p=0.04		p<0.001
Comorbidities$^{\phi}$										
No	33 (64.7)	124 (57.1)	90 (61.6)	162 (63.0)	42 (82.4)	179 (71.9)	29 (80.6)	52 (62.7)	194 (68.3)	517 (64.1)
Yes	18 (35.3)	93 (42.9)	56 (38.4)	95 (37.0)	9 (17.6)	70 (28.1)	7 (19.4)	31 (37.3)	90 (31.7)	289 (35.9)
		p=0.32		p=0.78		p=0.12		p=0.05		p=0.21
Knowledge BC is curable$^{\gamma}$										
Yes	35 (68.6)	181 (83.4)			22 (43.1)	105 (42.2)	21 (58.3)	63 (75.9)	78 (56.5)	349 (63.6)
No/Not know	16 (31.4)	36 (16.6)			29 (56.9)	144 (57.38)	15 (41.7)	20 (24.1)	60 (43.5)	200 (36.4)
		p=0.02				p=0.90		p=0.05		p=0.13
Stage at BC diagnosis										
I/II	20 (39.2)	77 (35.5)	67 (45.9)	110 (42.8)	11 (21.6)	85 (34.1)	10 (27.8)	32 (38.6)	108 (38.0)	304 (37.7)
III	26 (51.0)	106 (48.9)	61 (41.8)	113 (44.0)	26 (51.0)	110 (44.2)	15 (41.7)	30 (36.1)	128 (45.1)	359 (44.5)

	Namibia (n=268)		South Africa (n=403)		Uganda (n=300)		Zambia (n=199)		All sites (n=1090)	
	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-
Characteristic	**N (%[α])**	**N (%[α])**	**N (%[α])**	**N (%[α])**	**N (%[α])**	**N (%[α])**	**N (%[α])**	**N (%[α])**	**N (%[α])**	**N (%[α])**
IV	5 (9.8)	34 (15.6)	18 (12.3)	34 (13.2)	8 (15.7)	45 (18.1)	3 (8.3)	5 (6.0)	34 (12.0)	118 (14.6)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	6 (11.7)	9 (3.6)	8 (22.2)	16 (19.3)	14 (4.9)	25 (3.1)
		p=0.56		p=0.83		p=0.04		p=0.72		p=0.38
Tumour grade										
1	8 (15.7)	36 (16.6)	11 (7.5)	11 (4.3)	6 (11.8)	45 (18.1)	1 (2.8)	8 (9.6)	26 (9.2)	100 (12.4)
2	16 (31.4)	80 (36.9(	75 (51.4)	115 (44.8)	9 (17.7)	41 (16.5)	11 (30.6)	18 (21.7)	111 (39.0)	254 (31.5)
3	15 (29.4)	51 (23.5)	51 (34.9)	119 (46.3)	13 (25.5)	53 (21.3)	7 (19.4)	17 (20.5)	86 (30.3)	240 (29.8)
Unspecified	12 (23.5)	50 (23.0)	9 (6.2)	12 (4.6)	23 (45.1)	110 (44.2)	17 (47.2)	40 (48.2)	61 (21.5)	212 (26.3)
		p=0.81		p=0.12		p=0.71		p=0.50		p=0.06
Receptor subtype[φ]										
HR+, HER2-	22 (43.1)	102 (47.0)	16 (11.0)	27 (10.5)					38 (19.3)	129 (27.2)
HR+, HER2+	15 (29.4)	49 (22.6)	80 (54.8)	156 (60.7)					95 (48.3)	205 (43.3)
HR-, HER2+	2 (3.9)	20 (9.2)	17 (11.6)	26 (10.1)					19 (9.6)	46 (9.7)
HR-, HER2-	11 (21.6)	34 (15.7)	29 (19.9)	37 (14.4)					40 (20.3)	71 (15.0)
Unknown	1 (2.0)	12 (5.5)	4 (2.7)	11 (4.2)					5 (2.5)	23 (4.9)
		p=0.38		p=0.55						p=0.08
ART use										
No	2 (3.9)		38 (26.0)		4 (7.8)		2 (5.5)		46 (16.2)	
Yes	47 (92.2)		107 (73.3)		36 (70.6)		32 (89.0)		222 (78.2)	
Unknown	2 (3.9)		1 (0.7)		11 (21.6)		2 (5.5)		16 (5.6)	

[δ]Socio economic position (SEP) was derived from a score of combined self-reported access to amenities including home ownership, indoor water, flush toilet, electricity, vehicle, refrigerator, landline, gas or electric stove and a bed. SEP categories (low, medium, or high) were constructed based on country specific distribution of the SEP tertiles.

[ϕ]Comorbidities include: Tuberculosis, Hepatitis, Hypertension, Heart disease, Diabetes, Anaemia, COPD, Asthma, other cancer, other infections and other diseases.

[γ]Data on this variable was not available for South Africa because a different questionnaire was used at this site.

[φ]Data on tumour molecular subtypes were available for Namibia and South Africa only.

Supplementary Figure 7.1 UNAIDS HIV estimates showing age-specific mortality rates in the HIV-infected (female) population for the countries of the ABC-DO participating sites