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# Impact of HIV infection on survival among women with stage I-III breast cancer: Results from the South African breast cancer and HIV outcomes study

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## Abstract

In some countries of sub-Saharan Africa, the prevalence of HIV exceeds 20%; in South Africa, 20.4% of people are living with HIV. We examined the impact of HIV infection on the overall survival (OS) of women with nonmetastatic breast

**Abbreviations:** ABC-DO, African Breast Cancer Disparity in Outcomes; ART, antiretroviral therapy; BC, breast cancer; BMI, body mass index; CHBAH, Chris Hani Baragwanath Academic Hospital; CI, confidence interval; CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HICs, high income countries; HIV, human immunodeficiency virus; HR, hazard ratio; IQR, interquartile range; OR, odds ratio; OS, overall survival; PLWH, people living with HIV; PR, progesterone receptor; SABCHO, South African Breast Cancer and HIV Outcomes Study; SSA, sub-Saharan Africa; WLWH, women living with HIV.

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cancer (BC) enrolled in the South African Breast Cancer and HIV Outcomes (SABCHO) study. We recruited women with newly diagnosed BC at six public hospitals from 1 July 2015 to 30 June 2019. Among women with stages I-III BC, we compared those with and without HIV infection on sociodemographic, clinical, and treatment factors. We analyzed the impact of HIV on OS using multivariable Cox proportional hazard models. Of 2367 women with stages I-III BC, 499 (21.1%) had HIV and 1868 (78.9%) did not. With a median follow-up of 29 months, 2-year OS was poorer among women living with HIV (WLWH) than among HIV-uninfected women (72.4% vs 80.1%, $P < .001$; adjusted hazard ratio (aHR) 1.49, 95% confidence interval (CI) = 1.22-1.83). This finding was consistent across age groups ≥45 years and <45 years, stage I-II BC and stage III BC, and ER/PR status (all $P < .03$). Both WLWH with <50 viral load copies/mL and WLWH with ≥50 viral load copies/mL had poorer survival than HIV-uninfected BC patients [aHR: 1.35 (1.09-1.66) and 1.54 (1.20-2.00), respectively], as did WLWH who had ≥200 CD4+ cells/mL at diagnosis [aHR: 1.39 (1.15-1.67)]. Because receipt of antiretroviral therapy has become widespread, WLWH is surviving long enough to develop BC; more research is needed on the causes of their poor survival.

**KEYWORDS**
breast cancer, HIV, overall survival, South Africa

**What's new?**

Breast cancer patients living with HIV are a growing population globally. Associations between HIV status and breast cancer subtype, treatment and survival, however, remain unclear. In this investigation of women with nonmetastatic breast cancer in South Africa, patients living with HIV at breast cancer diagnosis were found to be at significantly greater risk of death from any cause than non-HIV-infected women with breast cancer. This finding persisted after accounting for differences in age, ethnicity, cancer stage, cancer subtype and treatments received. The findings cast light on adverse impacts linked to HIV infection in nonmetastatic breast cancer patients, despite antiretroviral therapy.

## 1 | INTRODUCTION

Of the estimated 36.7 million people living with HIV worldwide, 7 million (19%) live in South Africa.[1] The rollout of effective antiretroviral therapy (ART) has markedly increased their life expectancy, but as they age, the burden of breast cancer (BC) among them has risen.[2,3]

Several retrospective studies from the United States have shown that HIV infection adversely affects BC survival.[4–6] In 2019, Coghill et al showed that women living with HIV (WLWH) who were diagnosed with stages I-III BC had worse mortality than HIV-uninfected women; their absolute mortality rates were 41.7% vs 15.8% [hazard ratio (HR) 1.85, 95% confidence interval (CI) 1.68-2.04].[4]

Although BC survival data from Africa are sparse, the African Breast Cancer-Disparities in Outcomes (ABC-DO) study estimated the 3-year overall survival (OS) of 2156 women with BC from five countries in sub-Saharan Africa (SSA) to be 50% (95% CI 48-53), while BC 5-year survival is >80% in high-income countries (HICs).[7,8] In a meta-analysis of BC outcomes in SSA, Brandão et al showed that WLWH was diagnosed with BC at a more advanced stage and had worse OS (HR: 1.43; 95% CI: 1.06-1.92) than HIV-uninfected women.[9] We have found no data on receipt of BC treatment and ART, viral loads or CD4 counts among WLWH with BC in SSA.

Since July 2015, the South African Breast Cancer and HIV Outcomes (SABCHO) Study has been prospectively enrolling women newly diagnosed with BC at six public academic hospitals located within Gauteng and KwaZulu-Natal provinces in South Africa.[10] The primary aims of the SABCHO study are to examine the impact of HIV on BC survival and to investigate possible reasons for survival disparities. We have found that WLWH is diagnosed with BC at a younger age and are less likely to achieve a pathological complete response after neoadjuvant chemotherapy than others,[10–12] but we have not found associations of HIV status with BC subtype or the quality of treatment received. We previously found that HIV status was not associated with survival among women with stage IV BC.[13] In this article, we report our findings regarding patients diagnosed with nonmetastatic BC.

**TABLE 1** Sociodemographic and premorbid characteristics of women with stages I-III breast cancer in the SABCHO cohort by HIV status

| | HIV negative | HIV positive | Total | *P*-value |
|---|---|---|---|---|
| HIV status (row %) | 1868 (78.9%) | 499 (21.1%) | 2367 (100.0%) | |
| Age at diagnosis in years | | | | |
| <40 | 198 (10.6) | 128 (25.7) | 326 (13.8) | <.001 |
| 40-49 | 359 (19.2) | 209 (41.9) | 568 (24.0) | |
| 50-59 | 441 (23.6) | 116 (23.2) | 557 (23.5) | |
| 60-69 | 463 (24.8) | 36 (7.2) | 499 (20.1) | |
| ≥70 | 407 (21.8) | 10 (2.0) | 417 (17.6) | |
| Age at diagnosis in years, Median (IQR)[a] | 58.8 (48.0-68.3) | 45.0 (39.6-52.4) | 55.1 (44.8-65.8) | <.001 |
| Menopausal status | | | | |
| Premenopausal | 543 (29.1) | 308 (61.7) | 851 (36.0) | <.001 |
| Menopausal | 1325 (70.9) | 191 (38.3) | 1516 (64.0) | |
| Ethnicity | | | | |
| Black | 1358 (72.7) | 487 (97.6) | 1845 (77.9) | <.001 |
| Asian | 245 (13.1) | 2 (0.4) | 247 (10.4) | |
| White | 172 (9.2) | 0 (0.0) | 172 (7.3) | |
| Mixed ethnic | 93 (5.0) | 10 (2.0) | 103 (4.4) | |
| Highest level of education | | | | |
| Primary education and below | 558 (30.2) | 101 (20.8) | 659 (28.2) | <.001 |
| Secondary education and above | 1292 (69.8) | 393 (79.2) | 1685 (71.8) | |
| Wealth index | | | | |
| 1 | 313 (16.8) | 158 (31.7) | 471 (19.9) | <.001 |
| 2 | 347 (18.6) | 130 (26.1) | 477 (20.2) | |
| 3 | 381 (20.4) | 93 (18.6) | 474 (20.0) | |
| 4 | 413 (21.1) | 64 (12.8) | 477 (20.2) | |
| 5 (Wealthiest) | 414 (22.2) | 54 (10.8) | 468 (19.8) | |
| Alcohol | | | | |
| Yes | 342 (18.4) | 120 (24.1) | 462 (19.6) | .004 |
| No | 1521 (81.6) | 377 (75.9) | 1898 (980.4) | |
| Smoking | | | | |
| Yes | 265 (14.2) | 41 (8.3) | 306 (13.0) | <.001 |
| No | 1598 (85.8) | 456 (91.7) | 2054 (87.0) | |
| BMI | | | | |
| <25 | 280 (15.8) | 131 (27.4) | 411 (18.2) | <.001 |
| 25-29.9 | 457 (25.7) | 138 (28.9) | 595 (26.4) | |
| ≥30 | 1038 (58.5) | 209 (43.7) | 1247 (55.3) | |
| Diabetes | | | | |
| Yes | 300 (16.1) | 21 (4.2) | 321 (13.6) | <.001 |
| No | 1563 (83.9) | 476 (95.8) | 2039 (86.4) | |
| Hypertension | | | | |
| Yes | 871 (46.8) | 106 (21.3) | 977 (41.4) | <.001 |
| No | 992 (53.2) | 391 (78.7) | 1383 (58.6) | |
| Cerebrovascular disease | | | | |
| Yes | 137 (7.4) | 10 (2.0) | 147 (6.2) | <.001 |
| No | 1726 (92.6) | 487 (98.0) | 2213 (93.8) | |
| ECOG PS | | | | |
| 0 and 1 | 1738 (93.3) | 484 (97.2) | 2222 (94.1) | .001 |
| 2-4 | 125 (6.7) | 14 (2.8) | 139 (5.9) | |

(Continues)

**TABLE 1** (Continued)

| | HIV negative | HIV positive | Total | *P*-value |
|---|---|---|---|---|
| Hospitals | | | | |
| CHBAH | 699 (37.4) | 225 (45.1) | 924 (39.0) | <.001 |
| CMJAH | 503 (26.9) | 101 (20.2) | 604 (25.5) | |
| Durban | 339 (18.1) | 60 (12.0) | 399 (16.9) | |
| Grays | 398 (16.0) | 93 (18.7) | 391 (16.5) | |
| Ngwelezana | 29 (1.6) | 20 (4.0) | 49 (2.1) | |

*Note*: Missing data: the highest level of education (n = 23), alcohol (n = 7), smoking (n = 7), BMI (n = 114), diabetes (n = 7), hypertension (n = 7), cerebrovascular disease (n = 7) and ECOG (n = 6).
Abbreviations: BMI, body mass index; CHBAH, Chris Hani Baragwanath Academic Hospital; CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; PS, performance status at baseline.

## 2 | METHODS

### 2.1 | Context and settings

South Africa is an upper-middle-income country, but despite socio-economic improvements since 1994 (the post-apartheid era), high levels of inequality, unemployment and poverty persist, adversely affecting the 80% majority black population.[14] South Africa has dual healthcare systems. The wealthiest fifth of the population is privately insured; the remaining 80% are dependent on the resource-constrained public health care system.[15] In the SABCHO study, we enrolled subjects from the breast units of six public tertiary referral hospitals: Chris Hani Baragwanath Academic Hospital (CHBAH), Soweto, Johannesburg; Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Johannesburg; Inkosi Albert Luthuli Central Hospital, Durban; Addington Hospital, Durban; Gray's Hospital, Pietermaritzburg; and Ngwelezana Hospital, Empangeni. The two hospitals in Durban share facilities and staff and are analyzed here as a single unit.

In 2015, when our study began, national guidelines recommended antiretroviral therapy (ART) initiation for all people living with HIV (PLWH) whose CD4 counts were <350 cells/mL. All PLWH with a new cancer diagnosis were also initiated on ART irrespective of their CD4 count. In September 2016, South Africa adopted the universal-test-and-treat policy.

Cancer surgery is available in the district and tertiary provincial hospitals. Chemotherapy, radiation therapy and endocrine therapy are available at tertiary referral hospitals; treatment costs to patients are low or waived according to income. Both breast conserving surgery and total mastectomy are offered at all study sites. The most common BC chemotherapy regimen in our hospitals is a combination of anthracycline and cyclophosphamide, with or without 5-fluorouracil and usually followed by a taxane. Human epidermal growth factor receptor-2 (HER2)-targeted agents were not available during our study period.

### 2.2 | Participants

Between 1 July 2015 and 30 June 2019, we recruited as SABCHO participants all women >18 years of age, recently diagnosed with histologically confirmed invasive BC, residing in South Africa for ≥5 years, free of a self-reported prior cancer diagnosis (excluding in situ cervical cancer and nonmelanoma skin cancer), and providing written informed consent. For this analysis, we included only patients with known HIV status, American Joint Committee on Cancer (AJCC) seventh edition stage I-III disease and known tumor receptor (estrogen, progesterone and HER2) status. We categorized all cases by tumor receptor expression as estrogen receptor (ER)+/progesterone receptor (PR)+/HER2−, ER+/PR+/HER2+, ER−/PR−/HER2+ and ER−/PR−/HER2−. For the purpose of our analysis, we classified the 105 women (4.4%) who had equivocal HER2 testing (ie, HER2+ by immunohistochemistry with missing confirmatory HER2 fluorescence in situ hybridization testing) as HER2 negative. These women were enrolled before HER2-targeted treatment became available in our hospitals. We excluded patients with bilateral BC because we could not differentiate them from patients with de novo metastatic disease.

### 2.3 | Data collection and processing

Data on sociodemographics (ie, age, self-reported ethnicity [black, Asian, white and mixed ethnic], marital status, the highest level of education, employment status), height, weight, comorbidities, clinical tumor size, nodal status, tumor grade, ER/PR and HER2 status were collected at diagnosis. We derived a wealth index from the principal component analysis of a survey of household possessions and facilities, as previously described,[16] grouping patients into quintiles based on their wealth index ranking. For all patients, BC staging work-up at diagnosis included: full blood count; electrolytes, urea and creatinine; liver function tests; chest X-ray and abdominal ultrasound. Patients who presented with symptoms and signs suggestive of metastatic disease underwent computerized tomography scans and bone scans; patients with confirmed stage IV disease at diagnosis were excluded from this analysis. Treatment data were collected directly from the medical record.

Participants were grouped and analyzed based on their HIV status. Those who did not report that they were living with HIV were tested for HIV at BC diagnosis, after providing consent. HIV testing was performed using the enzyme-linked immunosorbent assay through the National Health Laboratory Services. Approximately 4.7%

**TABLE 2** Clinical characteristics at diagnosis and treatment of women with stages I-III breast cancer in the SABCHO cohort by HIV status

| | HIV negative | HIV positive | Total | *P*-value |
|---|---|---|---|---|
| HIV status (row %) | 1868 (78.9%) | 499 (21.1%) | 2367 (100.0%) | |
| Tumor stage | | | | |
| T0 | 4 (0.2) | 1 (0.2) | 5 (0.2) | .401[a] |
| T1 | 201 (10.8) | 41 (8.2) | 242 (10.2) | |
| T2 | 820 (43.9) | 212 (42.5) | 1032 (43.6) | |
| T3 | 300 (16.1) | 88 (17.6) | 388 (16.4) | |
| T4 | 543 (29.1) | 157 (31.5) | 700 (29.6) | |
| Nodal stage | | | | |
| 0 | 649 (34.7) | 132 (26.5) | 781 (33.0) | |
| 1 | 772 (41.3) | 226 (45.3) | 998 (42.2) | |
| 2 | 362 (19.4) | 109 (21.8) | 471 (19.9) | |
| 3 | 85 (4.6) | 32 (6.4) | 117 (4.9) | |
| Stage | | | | |
| Stage I | 142 (7.6) | 23 (4.6) | 165 (7.0) | **.017** |
| Stage II | 819 (43.8) | 206 (41.3) | 1025 (43.3) | |
| Stage III | 907 (48.6) | 270 (54.1) | 1177 (49.7) | |
| Histological diagnosis | | | | |
| Invasive ductal | 1782 (95.4) | 483 (96.8) | 2265 (95.7) | .172 |
| Other histological type | 86 (4.6) | 16 (3.2) | 102 (4.3) | |
| Grade | | | | |
| Grade 1 | 123 (7.7) | 30 (7.0) | 153 (7.5) | .883 |
| Grade 2 | 880 (55.0) | 239 (55.7) | 1119 (55.1) | |
| Grade 3 | 598 (37.3) | 160 (36.3) | 758 (37.3) | |
| Breast cancer subtype | | | | |
| ER+ or PR+/HER2− | 1163 (62.3) | 271 (54.3) | 1434 (60.6) | **.003** |
| ER+/PR+/HER2+ | 299 (16.0) | 111 (22.2) | 410 (17.3) | |
| ER−/PR−/HER2+ | 117 (6.3) | 31 (6.2) | 148 (6.3) | |
| ER−/PR−/HER2− | 289 (15.5) | 86 (17.2) | 375 (15.8) | |
| Ki67 | | | | |
| <20 | 581 (32.3) | 130 (27.3) | 711 (31.2) | **.036** |
| ≥20 | 1220 (67.7) | 347 (72.7) | 1567 (68.8) | |
| Surgical treatment | | | | |
| No | 434 (23.2) | 137 (27.5) | 571 (24.1) | .050 |
| Yes | 1434 (76.8) | 362 (72.5) | 1796 (75.9) | |
| Chemotherapy treatment | | | | |
| No | 522 (27.9) | 88 (17.6) | 610 (25.8) | **<.001** |
| Yes | 1346 (72.1) | 411 (82.4) | 1757 (74.2) | |
| Radiation therapy | | | | |
| No | 893 (47.8) | 248 (49.7) | 1141 (48.2) | .452 |
| Yes | 975 (52.2) | 251 (50.3) | 1226 (51.8) | |
| Treatment received | | | | |
| Surgery, no chemotherapy | 303 (16.2) | 40 (8.1) | 343 (14.5) | **<.001** |
| Surgery + chemotherapy | 1131 (60.5) | 322 (65.5) | 1453 (61.4) | |
| Chemotherapy, no surgery | 215 (11.5) | 89 (17.8) | 304 (12.8) | |
| No surgery or chemotherapy | 219 (11.7) | 48 (9.6) | 267 (11.3) | |

(Continues)

**TABLE 2** (Continued)

| | HIV negative | HIV positive | Total | *P*-value |
|---|---|---|---|---|
| Endocrine therapy (ER+/PR+ patients only, N = 1844) | | | | |
| No | 252 (17.2) | 81 (21.2) | 333 (18.1) | .073 |
| Yes | 1210 (82.8) | 301 (78.8) | 1511 (81.9) | |
| Median follow-up time in months (IQR) | 29.0 (19.0-42.0) | 26.0 (17.0-38.0) | 29.0 (19.0-41.0) | **<.001** |

*Note*: Missing data: Grade (n = 337), Ki67 (n = 89). *P*-value < .05 shown in bold face.
Abbreviations: ER/PR, estrogen receptor/progesterone receptor; HER2, human epidermal growth factor receptor 2; IQR interquartile range.
[a]Fisher's exact test.

of women in our cohort had unknown HIV status and were excluded from the analysis.[17] Repeat negative tests were not mandatory for the HIV-uninfected cohort at any time during the follow-up period. Repeat testing was ordered at the discretion of the managing physician with the consent of the patient.

## 2.4 | Outcome variables

Our primary outcome was OS defined as the time from the date of BC diagnosis to the date of death, the date on which the participant was last known to be alive, or our administrative censoring date (30 September 2020).[18] Patients were contacted every 3 months after enrolment to determine vital status. If we were unable to reach the patient, her next of kin or other persons whom she named as close contacts for two consecutive follow-up calls, we searched Verify ID (a publicly available administrative database) to determine the patient's vital status (Death certification is mandatory for everyone dying in South Africa regardless of cause or place of death). In a quality control analysis, we found 100% agreement between the publicly available administrative data and our own data for patients whose date of death we had documented.

Patients were censored at the last date when they were known to be alive. Sources of the date of death information were 70.7% from next of kin, 7.0% from hospital records and 22.3% from publicly available administrative data. There were no differences in the source of death data by HIV status.

## 2.5 | Statistical analysis

We compared the distribution of the categorical and continuous variables by HIV status, using Pearson's chi-squared test or the Wilcoxon Rank Sum test as appropriate. We constructed Kaplan-Meier survival curves stratified by HIV status for the overall cohort and subgrouped by age, stage at diagnosis and ER/PR status. We dichotomized the age variable using the median age of WLWH in our cohort and compared women ≤45 years and >45 years. Survival comparisons were performed using the log-rank test.

We tested the association of the variables with OS in a univariate proportional hazards model. We then constructed a multivariable Cox proportional hazards model to investigate the effect of HIV status on OS, while adjusting for the effects of other demographic and clinical characteristics. In that model, we included covariates known a priori to impact BC survival [age, ECOG performance status at diagnosis,[19] clinical stage (I and II vs III),[7] receptor subtype (ER+/PR+/HER2− and ER+/PR+/HER2+ vs ER−/PR−/HER2+ and ER−/PR−/HER2−),[20] Ki67 score (<20% vs ≥20%)[21] and treatment received (surgery and chemotherapy vs surgery/no chemotherapy vs chemotherapy/no surgery vs no surgery or chemotherapy)[22,23]]. Additional variables showing an association with OS in the univariate analysis with a significance of $P < .1$ and not part of the a priori set of covariates were also included in the multivariable model; these included ethnicity, highest level of education achieved and body mass index (BMI). We examined hazard ratios for HIV before and after adjustment for these variables to identify both confounding effects (eg, age, stage) and mediating pathways (eg, BC receptor subtypes). We excluded tumor grade due to a high number of missing values; wealth index because of collinearity with ethnicity and educational status; diabetic and cerebrovascular disease because of their low prevalence in WLWH; and radiation therapy because of the indications varied based on both indication and scheduled dose. Among WLWH, we compared OS within subgroups based on the use of ART (yes/no), HIV viral load (<50 vs ≥50 copies/mL) and CD4 cell count (<200 vs ≥ 200 cells/mL) at BC diagnosis. All statistical analyses were performed using Stata version 16 (StataCorp Ltd, College Station, TX).

# 3 | RESULTS

Between 1 July 2015 and 30 June 2019, we enrolled 2995 women into the SABCHO study. Of these, we excluded 26 (<1%) women with missing clinical stage, 523 (17.5%) diagnosed with stage IV BC, 23 (<1%) with unknown HIV status, 8 (<1%) with unknown hormone receptor status and 48 (<1%) with bilateral BC. Table 1 shows the sociodemographic and comorbidity characteristics of the remaining 2367 women. The 499 (21.1%) WLWH were younger than the 1868 (78.9%) without HIV [Median age (interquartile range): 45.0 (39.6-52.4) vs 58.8 (48.0-68.3), $P < .001$]. Compared to HIV-uninfected women, WLWH were less wealthy and more likely to be of black African descent, educated beyond the primary level, of normal body size (BMI <25 kg/m$^2$; $P < .001$ for all comparisons). They were less likely to report having diabetes, hypertension or cerebrovascular disease ($P < .001$ for all comparisons; Table 1); these differences

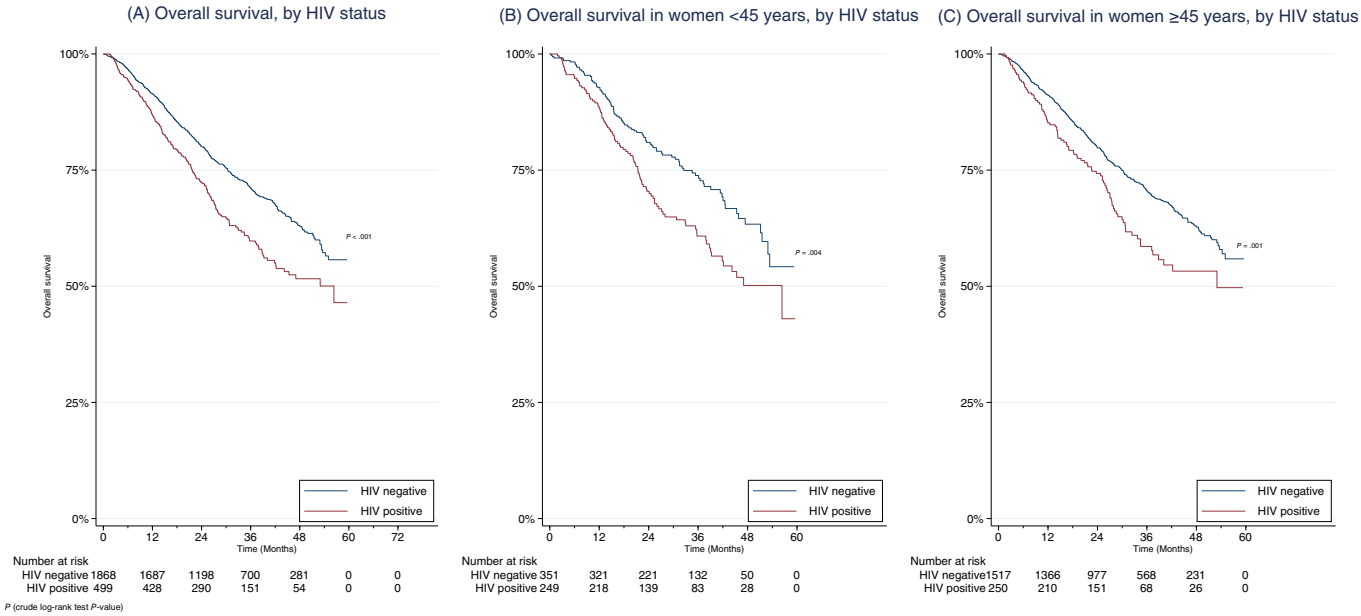



**FIGURE 1** Overall survival in women with stages I-III breast cancer enrolled in the SABCHO cohort by HIV status and by age group [Color figure can be viewed at wileyonlinelibrary.com]

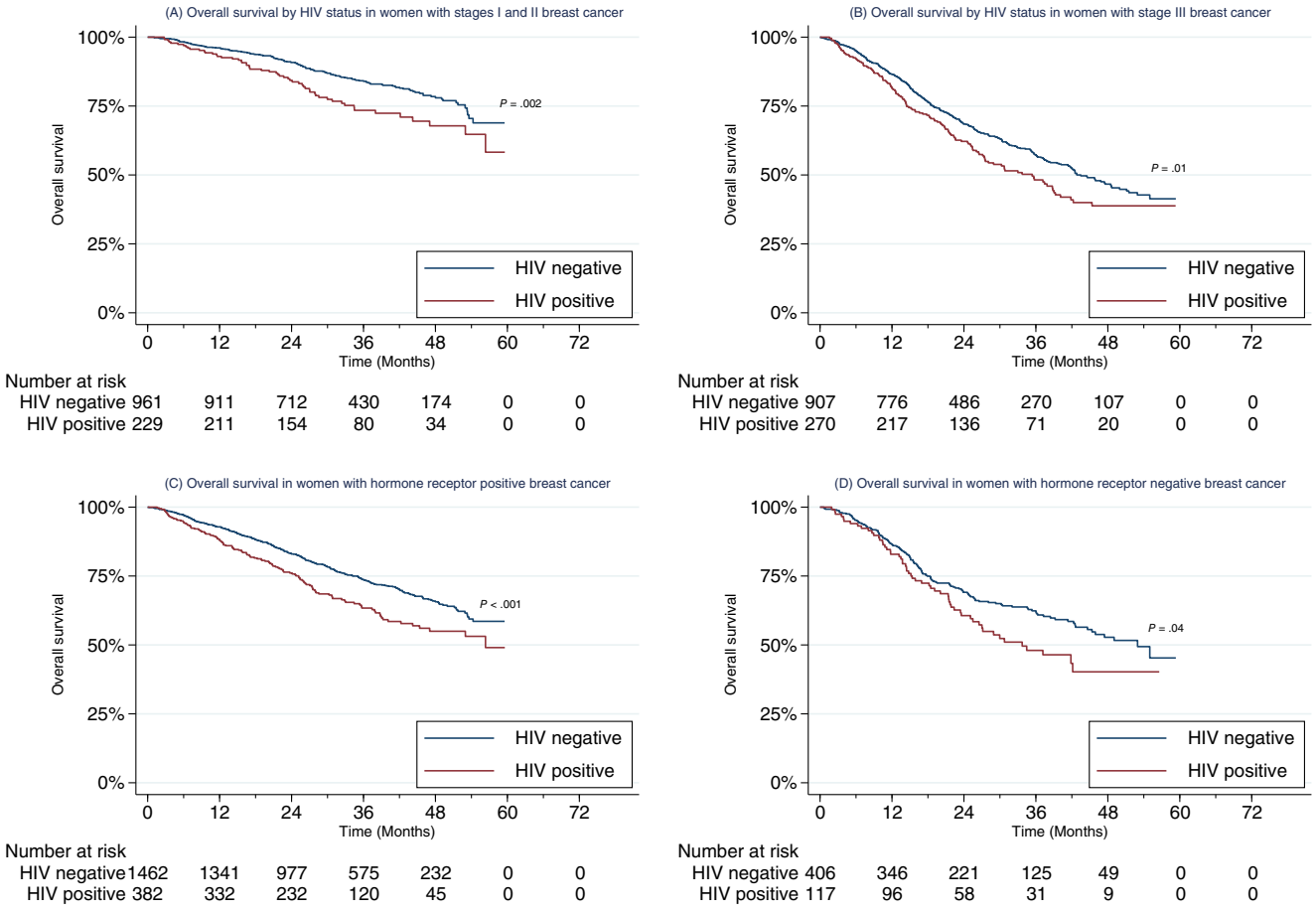



**FIGURE 2** Overall survival in women with stages I-III breast cancer enrolled in the SABCHO cohort by (A) and (B) HIV status and stage, and (C) and (D) HIV status and breast cancer hormone receptor status [Color figure can be viewed at wileyonlinelibrary.com]

persisted when we restricted the analysis to women ≥45 years of age (data not shown).

Overall, nearly half the women presented with stage III BC, but WLWH were more likely than others to have stage III disease ($P = .017$). WLWH were also more likely to receive chemotherapy (82.4%) than HIV-uninfected women (72.1%, $P < .001$) overall (Table 2), among those with stage I-II BC (76.0% vs 64.5%, $P = .001$) and those with stage III BC (87.8% vs 80.4%, $P = .004$; Table S1).

**TABLE 3** Multivariate Cox proportional hazard ratio model of risk factors for mortality in women with stages I-III breast cancer enrolled in the SABCHO cohort

| | Died, N = 728 (row %) | Hazard ratio (95% CI) | *P*-value |
|---|---|---|---|
| HIV | | | |
| Negative | 538 (28.8) | 1.00 (Reference) | |
| Positive | 190 (38.1) | 1.49 (1.22-1.83) | **<.001** |
| Age at diagnosis in years | | | |
| <40 | 109 (33.4) | 1.00 (Reference) | |
| 40-49 | 160 (28.2) | 0.84 (0.64-1.08) | .173 |
| 50-59 | 155 (27.8) | 0.84 (0.64-1.10) | .207 |
| 60-69 | 137 (27.4) | 0.86 (0.64-1.16) | .330 |
| ≥70 | 167 (40.1) | 0.95 (0.69-1.31) | .771 |
| Ethnicity | | | |
| Others | 137 (26.2) | 1.00 (Reference) | |
| Black | 591 (32.0) | 1.01 (0.81-1.24) | .954 |
| Highest level of education | | | |
| Primary education and below | 247 (37.5) | 1.00 (Reference) | |
| Secondary education and above | 466 (27.7) | 0.73 (0.61-0.88) | **.001** |
| Body mass index (BMI) | | | |
| <25 | 154 (37.5) | 1.00 (Reference) | |
| 25-29.9 | 155 (26.1) | 0.76 (0.60-0.96) | **.020** |
| ≥30 | 376 (30.2) | 0.95 (0.78-1.18) | .663 |
| ECOG PS | | | |
| 0 and 1 | 643 (28.9) | 1.00 (Reference) | |
| 2-4 | 82 (59.0) | 1.73 (1.29-2.32) | **<.001** |
| Stage at diagnosis | | | |
| I and II | 214 (18.0) | 1.00 (Reference) | |
| III | 514 (43.7) | 2.13 (1.77-2.56) | **<.001** |
| Breast cancer subtype | | | |
| ER+/PR+/HER2− | 385 (26.8) | 1.00 (Reference) | |
| ER+/PR+/HER2+ | 133 (32.4) | 1.19 (0.96-1.47) | .106 |
| ER−/PR−/HER2+ | 57 (38.5) | 1.45 (1.06-1.97) | **.019** |
| ER−/PR−/HER2− | 153 (40.8) | 1.78 (1.44-2.19) | **<.001** |
| Ki67 | | | |
| <20 | 174 (24.5) | 1.00 (Reference) | |
| ≥20 | 520 (33.2) | 1.45 (1.20-1.75) | **<.001** |
| Treatment received | | | |
| Surgery + chemotherapy | 334 (23.0) | 1.00 (Reference) | |
| Surgery, no chemotherapy | 61 (17.8) | 1.19 (0.87-1.64) | .280 |
| Chemotherapy, no surgery | 189 (62.2) | 3.75 (3.07-4.58) | **<.001** |
| No surgery or chemotherapy | 144 (53.9) | 3.83 (2.98-4.92) | **<.001** |

*Note*: We tested for interactions between HIV and each of the above covariates, and none was statistically significant. Missing data: Highest level of education (n = 23), BMI (n = 114), ECOG (n = 6), Ki67 (n = 89). *P*-value < .05 shown in bold face.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER/PR, estrogen receptor/progesterone receptor; HER2, human epidermal growth factor receptor 2; PS, performance status.

**TABLE 4** HIV-related factors at diagnosis and hazard ratio for mortality in women with stages I-III breast cancer enrolled in the SABCHO cohort

| Characteristic | Died, *N = 728 (row %) | HR (95% CI) | *P*-value | HR (95% CI)[a] | *P*-value[a] |
|---|---|---|---|---|---|
| ART use | | | | | |
| HIV− | 538 (28.8) | 1.00 (Reference) | | 1.00 (Reference) | |
| HIV+, not on ART | 141 (36.1) | 1.76 (1.31-2.37) | **.001** | 1.68 (1.24-2.27) | **.001** |
| HIV+, on ART | 47 (46.1) | 1.37 (1.14-1.65) | **<.001** | 1.37 (1.12-1.66) | **.002** |
| HIV viral load (copies/mL) | | | | | |
| HIV− | 538 (28.8) | 1.00 (Ref) | | | |
| HIV+, VL < 50 | 112 (35.7) | 1.33 (1.09-1.64) | **.006** | 1.35 (1.09-1.66) | **.005** |
| HIV+, VL ≥ 50 | 70 (42.7) | 1.63 (1.27-2.09) | **<.001** | 1.54 (1.20-2.00) | **.001** |
| CD4 count (cells/mL) | | | | | |
| HIV− | 538 (28.8) | 1.00 (Ref) | | | |
| HIV+, CD4 ≥ 200 | 163 (37.3) | 1.40 (1.18-1.67) | **<.001** | 1.39 (1.15-1.67) | **<.001** |
| HIV+, CD4 < 200 | 18 (42.9) | 1.66 (1.04-2.66) | **.034** | 1.55 (0.96-2.48) | .070 |

*Note*: Missing data for *N: ART use (n = 2), HIV viral load (n = 8), CD4 count (n = 9). *P*-value < .05 shown in bold face.
Abbreviations: ART, antiretroviral therapy; VL, viral load.
[a]Adjusted for age and stage.

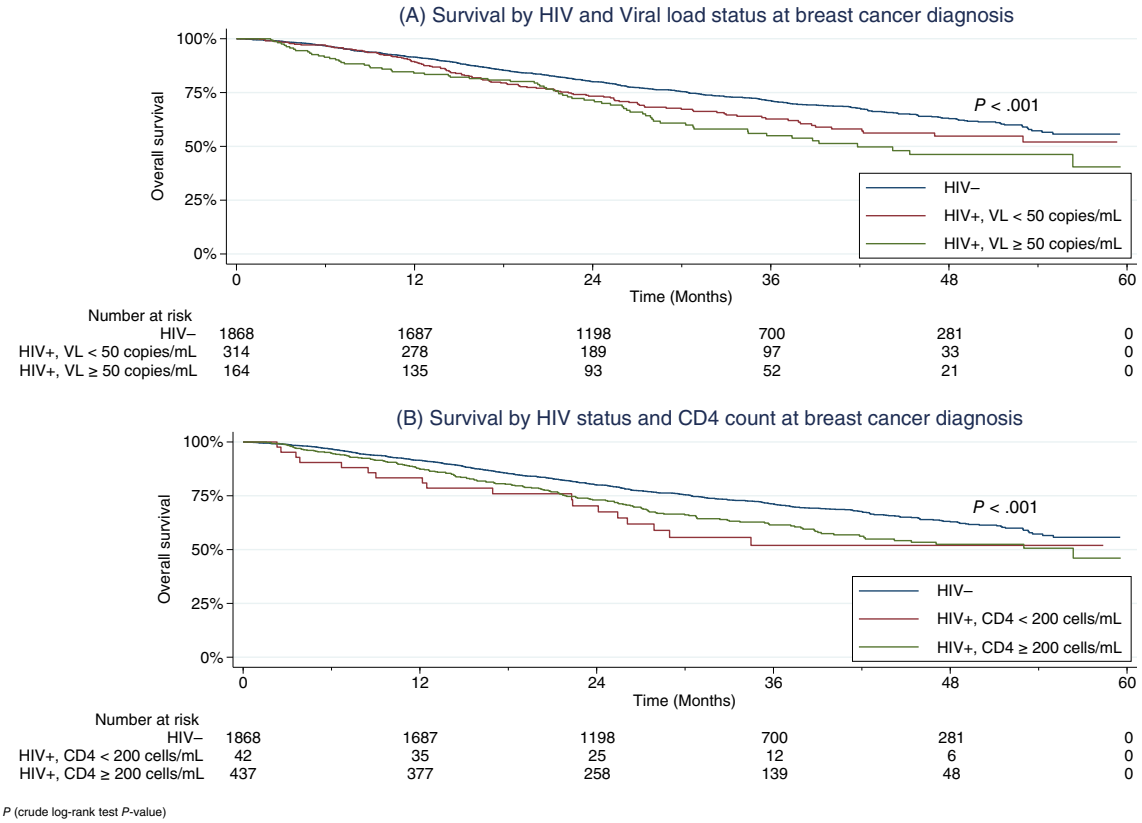



**FIGURE 3** Overall survival in women living with HIV with stages I-III breast cancer enrolled in the SABCHO cohort, by (A) viral load and (B) CD4 count at breast cancer diagnosis [Color figure can be viewed at wileyonlinelibrary.com]

By the median follow-up time of 29.0 months (IQR 19.0-41.0), 728 (30.8%) women had died. WLWH had poorer OS at 2 years than others (72.4% vs 80.1%, *P* < .001) overall, and in younger (age <45 years: 70.4% vs 81.0%, *P* = .004) and older age groups (≥45 years: 74.3% vs 79.9%, *P* = .001; Figure 1).

In addition, WLWH had poorer 2-year OS than HIV-uninfected women whether they had stage I-II disease (84.3% vs 90.8%, *P* = .002) or stage III disease (62.2% vs 68.6%, *P* = .011; Figure 2). WLWH also had poorer 2-year OS in both the ER+/PR+ (76.1% vs 83.1%, *P* < .001) and ER−/PR− (60.6% vs 69.1%, *P* = .037) subgroups (Figure 2).

In our univariate and multivariate model, all-cause mortality remained higher among WLWH than among HIV-uninfected women (Crude HR: 1.45, 95% CI: 1.23-1.72 and adjusted HR (aHR): 1.49, 95% CI: 1.22-1.83; Tables S2 and S3). Other predictors of survival were performance status, ECOG 2-4 vs 0-1 [aHR: 1.73 (1.29-2.32)]; stage III vs stages I and II BC [aHR: 2.13 (1.77-2.56)]; ER−/PR−/HER2+ [aHR: 1.45 (1.06-1.97)] and ER−/PR−/HER2− [aHR: 1.78 (1.44-2.19)] vs ER+/PR+/HER2− BC subtype; and Ki67 ≥ 20 vs <20 [aHR: 1.45 (1.20-1.75)]. Survival was worse among women who had chemotherapy with no surgery [aHR: 3.75 (3.07-4.58)] and women who had no surgery or chemotherapy [aHR: 3.83 (2.98-4.92)] than among women who had surgery with chemotherapy (Table 3). In a sensitivity analysis restricted to those who received surgery and at least some form of systemic therapy, the factors influencing OS were similar to those that did so in the full cohort (Table S3). In a sub-group analysis of WLWH only, significant predictors of survival were stage, hormone receptor status and Ki67 score [aHR for stage III vs stages I and II: 2.24 (1.53-3.28); aHR for ER−/PR−/HER2− vs ER+/PR+/HER2− BC subtype: 2.14 (1.37-3.36); and aHR for Ki67 score ≥20 vs <20:1.57 (1.03-2.38; Table S4)].

In exploratory analyses, both WLWH with <50 HIV copies/mL and WLWH with ≥50 copies/mL had greater mortality than HIV-uninfected BC patients [aHR: 1.35 (1.09-1.66), $P = .005$ and 1.54 (1.20-2.00), $P < .001$, respectively]. In addition, WLWH with ≥200 CD4+ cells/mL and those with <200 cells/mL both had worse OS than HIV-uninfected women [aHR: 1.39 (1.15-1.67), $P < .001$ and 1.55 (0.96-2.48), $P = .07$, respectively] (Table 4 and Figure 3).

## 4 | DISCUSSION

In our cohort of women with stages I-III BC at six public hospitals in South Africa, 21.1% were WLWH at BC diagnosis. At a median follow-up of 29.0 months, 2-year OS was 72.4% among WLWH vs 80.1% among HIV-uninfected women (aHR for all-cause mortality: 1.49, 95% CI 1.22-1.83). WLWH also had poorer OS within strata of age, stage and BC hormone receptor status.

Our findings are consistent with prior work from HICs demonstrating higher mortality rates among patients with BC and HIV than among HIV-uninfected BC patients.[4,24] In US National Cancer Database data from 2004 to 2014, mortality was higher among the 1197 BC patients with HIV than among the 1 448 757 HIV-uninfected BC patients (HR: 1.85; 95% CI 1.68-2.04). A recent meta-analysis of 18 studies (4 from North America, 14 from SSA) also found that WLWH and BC had poorer overall survival than HIV-uninfected women with BC, in both North America (HR: 2.45; 95% CI 1.11-5.41) and SSA (HR: 1.43; 95% CI 1.06-1.92).[9]

The reasons for these survival disparities are likely to be multifactorial. Many WLWH, both in South Africa and elsewhere, come from vulnerable populations at risk for poor cancer outcomes.[25–27] However, even controlling for age, ethnicity and education, our study found poorer survival among BC patients with than without HIV infection. Our models may not have controlled for unknown sociodemographic risk factors that may have affected access to high-quality BC treatment. Even so, our prior work on BC treatment quality in South Africa did not show any differences in receipt of timely adjuvant chemotherapy, endocrine therapy or radiotherapy based on HIV status.[28] WLWH in our cohort were more likely to have stage III disease, but they were also younger and therefore less likely to have slow-growing, ER+/PR+ BC.

The relative youth of the WLWH in our cohort is attributable to the younger age of WLWH in the general population. Breast cancer in younger women has a more aggressive phenotype than that in older women, with high proportions of ER/PR loss and HER2 overexpression.[29,30] Accordingly, younger age at diagnosis, especially of early-stage BC, is associated with poorer survival.[31,32] Even though our multivariable analyses adjusted for age, unknown factors related to age and HIV may have contributed to the survival disparity.

HER2-targeted agents, such as trastuzumab, were not available during our study period; adjuvant trastuzumab was added to the National Essential Medicines List in 2019. The lack of trastuzumab may have been of particular importance to the survival of WLWH, given that they were modestly more likely to have HER2+ BC. However, this discrepancy probably does not account for much of the difference in OS because we controlled for HER2 status in multivariable analysis, and because BC patients living with HIV also have poorer survival in high-income settings despite routine trastuzumab use.

Few studies have evaluated the association of comorbid HIV and malignancy with adherence to treatment of either condition. A nationwide study in Korea found that a cancer diagnosis was a risk factor for low ART adherence, and, among PLWH in SSA, increasing pill burden decreased ART adherence.[33,34] WLWH may also experience greater myelosuppression, and therefore more dose reductions or delays, than others from cytotoxic chemotherapy. Both incomplete adherence to endocrine therapy and reduced chemotherapy dose intensity can worsen BC outcomes[35,36]; we are currently investigating the impact of HIV on both of these aspects of BC treatment quality.

Comorbid HIV also may inhibit the immune response to breast tumors. Intraepithelial and stromal tumor-infiltrating lymphocyte density influences systemic therapy response and BC recurrence rates.[37,38] HIV also indirectly causes persistent immune activation via its effect on the gut, where acute infection damages tight junction proteins and promotes microbial dysbiosis.[39] Microbial gut translocation persists after viral suppression, contributing to a chronic pro-inflammatory state which may also increase the risk of BC progression and metastases.[40–42]

Finally, HIV increases risks for many competing causes of death unrelated to BC. The life expectancy of PLWH in South Africa has improved drastically in the past two decades, but even patients who initiate ART early have a 20% lower life expectancy than adults without HIV.[43,44] Cause of death data on our cohort members was not reliable enough to enable us to compute the exact proportions of excess deaths attributable to BC and of those due to complications of HIV.

However, our exploratory findings that even WLWH with HIV viral loads <50 copies/mL and CD4+ T-cell count ≥200 cells/mL had

worse survival suggests that HIV-related complications are not wholly responsible for the excess mortality observed in WLWH. Future work should include close monitoring of HIV indicators in patients undergoing BC treatment to determine if those cancer therapies lead to loss of HIV control and increase the risk of acute HIV-related events.

Most women in our cohort were diagnosed with stage III disease, but the proportion was higher among WLWH than among HIV-uninfected women (54.1% vs 48.6%). Several studies have found large proportions of advanced-stage disease at diagnosis and overall poor survival among BC patients in SSA.[7,45–47] Overall, our crude 2-year OS was 78.5% but 89.6% for women with stage I and II BC and 67.1% for those with stage III BC. Women with stage III BC in our cohort had a higher estimated 2-year OS than stage III BC patients in the overall ABC-DO cohort, and in the Nigeria and Uganda subcohorts (ABC-DO overall cohort: ~60%; Nigeria: ~50%; Uganda: ~56%).[7] However, in HICs, 5-year survival probability is ≥89%[8,48] among women diagnosed with early-stage BC. Some reasons for advanced-stage BC diagnosis in our setting include low BC awareness, difficulty in accessing healthcare, lack of population-based screening[49–51]; belief in alternative sources of healing and fear of conventional medicine[52,53]; and cumbersome referral pathways within the healthcare system.[50,54] The poor survival by stage of our WLWH (Figure 2) may be due in part to a higher risk of additional causes of death such as HIV-associated comorbidities and AIDS.

The survival pattern in our cohort shows that HIV has a later effect on survival in the ER−/PR− group than in the ER+/PR+ group. In the women with ER−/PR− BC, there was no significant disparity in survival between WLWH and HIV-uninfected women in the first 12 months of follow-up. In our prior work, we observed that WLWH had poorer responses to neoadjuvant chemotherapy than HIV-uninfected women. This effect was concentrated in the ER+/PR+ group; we found no difference in proportions with pathologic complete response between WLWH and HIV-negative women in the ER−/PR− group. We are currently analyzing endocrine therapy adherence among our WLWH and HIV-negative women.

Overall, our women who had chemotherapy with no surgery and those who had no surgery or chemotherapy had poorer survival than women who had both surgery and chemotherapy. This finding is expected. Patients who did not have surgery after chemotherapy probably had irresectable tumors or disease progression, or they abandoned treatment. The South African national policy specifies that low-cost or no-cost BC surgery, chemotherapy, radiotherapy and endocrine therapy should be available at tertiary public hospitals. However, resource constraints within the national health system mean that timely access to these treatments is inconsistent. We previously found that baseline care for our patients was reasonably concordant with the American Society of Clinical Oncology BC care quality measures for chemotherapy and endocrine therapy but poor for radiotherapy.[28] We lacked data to explain whether individual patients failed to receive surgery or chemotherapy because of lapses at the hospital level, incomplete patient adherence or clinically appropriate decisions after disease progression.

Strengths of our study include the large sample size of our cohort, the prospective multicenter design and the availability of detailed sociodemographic, clinical and outcome data, all unprecedented for a BC population from SSA. South Africa's high HIV prevalence and widespread access to ART make it an important setting for the study of HIV's impact on BC, and given our study's setting and multicentre design, our results are probably generalizable to SSA, the region with the world's largest absolute number of WLWH and comorbid BC.

Some limitations should be noted. We were not able to collect detailed information on HIV treatment or to assess treatment adherence, which may have differed by HIV status. We did not consider our information on disease-free survival and cause of death reliable enough to support analyses of the excess mortality seen in WLWH. Our median follow-up time was only 29 months, but the mortality we observed was higher than in most BC cohort studies in HICs.

## 5 | CONCLUSIONS

In the largest prospectively collected BC cohort, we know of describing survival in WLWH with BC, we found compelling evidence that WLWH had worse OS than HIV-uninfected women. Our study supports the conclusions of smaller studies from SSA and more precisely describes the survival disadvantages of WLWH.[4,5,24] The reasons why BC survival among WLWH is so poor call for further research focusing on differences in access to care, treatment-related adverse events, possible biological associations between HIV and tumor behavior and cause of death unrelated to BC but known to be associated with HIV, such as trauma, suicide, and specific complications of HIV/AIDs. In the future, we also hope to examine survival in South African BC patients diagnosed after 2019 to see to what extent access to trastuzumab ameliorated the OS disparity between women with and without HIV.

### CONFLICT OF INTEREST

Alfred I. Neugut have consulted for Otsuka, Eisai, GlaxoSmithKline, United Biosource Corp, Hospira, and also received grant support from Otsuka. Alfred I. Neugut is on the medical advisory board of EHE Intl. All other authors declare that they have no conflict of interest.

### AUTHOR CONTRIBUTIONS

The work reported in the paper has been performed by the authors, unless clearly specified in the text. *Conceptualization*: Maureen Joffe, Judith S. Jacobson, Alfred I. Neugut, Paul Ruff and Herbert Cubasch. *Data curation*: Oluwatosin A. Ayeni, Wenlong Carl Chen, Maureen Joffe, Sarah Nietz, Boitumelo Phakathi, Ines Buccimazza, Sharon Čačala, Laura W. Stopforth, Hayley A. Farrow and Herbert Cubasch. *Formal analysis*: Oluwatosin A. Ayeni, Daniel S. O'Neil, Wenlong Carl Chen, Tobias Chirwa and Valerie McCormack. *Funding acquisition*: Maureen Joffe, Judith S. Jacobson, Alfred I. Neugut, Paul Ruff and Herbert Cubasch. *Investigation*: Oluwatosin A. Ayeni, Maureen Joffe, Sarah Nietz, Boitumelo Phakathi, Ines Buccimazza, Sharon Čačala, Laura W. Stopforth and Herbert Cubasch. *Methodology*: Oluwatosin

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## ETHICS STATEMENT

The SABCHO study was approved by the University of the Witwatersrand Human Research Ethics Committee in Johannesburg, South Africa, and the Institutional Review Board of Columbia University in New York, NY. All participants provided written informed consent.

## DATA AVAILABILITY STATEMENT

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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## REFERENCES

1. UNAIDS. AIDS Data, 2016. https://www.unaids.org/sites/default/files/media_asset/global-AIDS-update-2016_en.pdf.
2. Grover S, Martei YM, Puri P, et al. Breast cancer and HIV in sub-Saharan Africa: a complex relationship. *J Glob Oncol*. 2017;4:1-11.
3. Prager GW, Braga S, Bystricky B, et al. Global cancer control: responding to the growing burden, rising costs and inequalities in access. *ESMO Open*. 2018;3:e000285.
4. Coghill AE, Han X, Suneja G, Lin CC, Jemal A, Shiels MS. Advanced stage at diagnosis and elevated mortality among US patients with cancer infected with HIV in the National Cancer Data Base. *Cancer*. 2019;125:2868-2876.
5. Coghill AE, Pfeiffer RM, Shiels MS, Engels EA. Excess mortality among HIV-infected individuals with cancer in the United States. *Cancer Epidemiol Biomarkers Prev*. 2017;26:1027-1033.
6. Coghill AE, Suneja G, Rositch AF, Shiels MS, Engels EA. HIV infection, cancer treatment regimens, and cancer outcomes among elderly adults in the United States. *JAMA Oncol*. 2019;5:e191742.
7. McCormack V, McKenzie F, Foerster M, et al. Breast cancer survival and survival gap apportionment in sub-Saharan Africa (ABC-DO): a prospective cohort study. *Lancet Glob Health*. 2020;8:e1203-e1212.
8. Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet*. 2018;391:1023-1075.
9. Brandão M, Bruzzone M, Franzoi M-A, et al. Impact of HIV infection on baseline characteristics and survival of women with breast cancer. *AIDS*. 2021;35:605-618.
10. Cubasch H, Ruff P, Joffe M, et al. South African breast cancer and HIV outcomes study: methods and baseline assessment. *J Glob Oncol*. 2017;3:114-124.
11. Phakathi B, Cubasch H, Nietz S, et al. Clinico-pathological characteristics among south African women with breast cancer receiving antiretroviral therapy for HIV. *Breast*. 2019;43:123-129.
12. Nietz S, O'Neil DS, Ayeni O, et al. A comparison of complete pathologic response rates following neoadjuvant chemotherapy among south African breast cancer patients with and without concurrent HIV infection. *Breast Cancer Res Treat*. 2020;184:861-872.
13. Pumpalova YS, Ayeni OA, Chen WC, et al. Impact of HIV infection on overall survival among women with stage IV breast cancer in South Africa. *Breast Cancer Res Treat*. 2021;189:285-296.
14. Francis D, Webster E. Inequality in South Africa. *Dev South Afr*. 2019;36:733-734.
15. Mayosi BM, Benatar SR. Health and health care in South Africa—20 years after Mandela. *N Engl J Med*. 2014;371:1344-1353.
16. O'Neil DS, Nietz S, Buccimazza I, et al. Neoadjuvant chemotherapy use for nonmetastatic breast cancer at five public south African hospitals and impact on time to initial cancer therapy. *Oncologist*. 2019;24:933-944.
17. Ayeni OA, Norris SA, Joffe M, et al. The multimorbidity profile of south African women newly diagnosed with breast cancer. *Int J Cancer*. 2020;147:361-374.
18. Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. *J Clin Oncol*. 2007;25:2127-2132.
19. Karakaya S, Karadağ İ, Duran AO, Oksuzoglu OB, Demirci U. Clinical outcomes and prognostic factors in HER-2 positive breast cancer with brain metastasis: a single-center experience. *J Clin Oncol*. 2020;38:e13015-e.
20. Johansson ALV, Trewin CB, Hjerkind KV, Ellingjord-Dale M, Johannesen TB, Ursin G. Breast cancer-specific survival by clinical subtype after 7 years follow-up of young and elderly women in a nationwide cohort. *Int J Cancer*. 2019;144:1251-1261.
21. Mannell A. The role of Ki-67 in breast cancer. *S Afr J Surg*. 2016;54:10-13.
22. Zarcos-Pedrinaci I, Redondo M, Louro J, et al. Impact of adjuvant chemotherapy on the survival of patients with breast cancer diagnosed by screening. *Cancer Med*. 2019;8:6662-6670.
23. Yin M, Verschraegen C, Vincent V-H, Patel SM, George T, Truica CI. Impact of lack of surgery on outcomes in elderly women with non-metastatic breast cancer—a surveillance, epidemiology, and end results 18 population based study. *Medicine*. 2020;99:e18745.
24. Coghill AE, Shiels MS, Suneja G, Engels EA. Elevated cancer-specific mortality among HIV-infected patients in the United States. *J Clin Oncol*. 2015;33:2376-2383.
25. Denning P, DiNenno E. Communities in crisis: is there a generalized HIV epidemic in impoverished urban areas of the United States. In XVIII international AIDS conference 2010:1.
26. Fox AM. The HIV-poverty thesis re-examined: poverty, wealth or inequality as a social determinant of HIV infection in sub-Saharan Africa? *J Biosoc Sci*. 2012;44:459-480.
27. Vaughan AS, Rosenberg E, Shouse RL, Sullivan PS. Connecting race and place: a county-level analysis of White, Black, and Hispanic HIV prevalence, poverty, and level of urbanization. *Am J Public Health*. 2014;104:e77-e84.
28. O'Neil DS, Chen WC, Ayeni O, et al. Breast cancer care quality in South Africa's public health system: an evaluation using American

society of clinical oncology/national quality forum measures. *J Glob Oncol*. 2019;5:1-16.
29. Anders CK, Hsu DS, Broadwater G, et al. Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression. *J Clin Oncol*. 2008;26:3324-3330.
30. Collins LC, Marotti JD, Gelber S, et al. Pathologic features and molecular phenotype by patient age in a large cohort of young women with breast cancer. *Breast Cancer Res Treat*. 2012;131:1061-1066.
31. Gnerlich JL, Deshpande AD, Jeffe DB, Sweet A, White N, Margenthaler JA. Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. *J Am Coll Surg*. 2009;208:341-347.
32. Fredholm H, Eaker S, Frisell J, Holmberg L, Fredriksson I, Lindman H. Breast cancer in young women: poor survival despite intensive treatment. *PLoS One*. 2009;4:e7695.
33. Kim J, Lee E, Park B-J, Bang JH, Lee JY. Adherence to antiretroviral therapy and factors affecting low medication adherence among incident HIV-infected individuals during 2009-2016: a nationwide study. *Sci Rep*. 2018;8:1-8.
34. Heestermans T, Browne JL, Aitken SC, Vervoort SC, Klipstein-Grobusch K. Determinants of adherence to antiretroviral therapy among HIV-positive adults in sub-Saharan Africa: a systematic review. *BMJ Glob Health*. 2016;1:e000125.
35. Zhang L, Yu Q, Wu X-C, et al. Impact of chemotherapy relative dose intensity on cause-specific and overall survival for stage I-III breast cancer: ER+/PR+, HER2− vs. triple-negative. *Breast Cancer Res Treat*. 2018;169:175-187.
36. Chirgwin JH, Giobbie-Hurder A, Coates AS, et al. Treatment adherence and its impact on disease-free survival in the breast international group 1-98 trial of tamoxifen and letrozole, alone and in sequence. *J Clin Oncol*. 2016;34:2452-2459.
37. Salgado R, Denkert C, Campbell C, et al. Tumor-infiltrating lymphocytes and associations with pathological complete response and event-free survival in HER2-positive early-stage breast cancer treated with lapatinib and trastuzumab: a secondary analysis of the NeoALTTO trial. *JAMA Oncol*. 2015;1:448-455.
38. Denkert C, von Minckwitz G, Darb-Esfahani S, et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. *Lancet Oncol*. 2018;19:40-50.
39. Zicari S, Sessa L, Cotugno N, et al. Immune activation, inflammation, and non-AIDS co-morbidities in HIV-infected patients under long-term ART. *Viruses*. 2019;11:200.
40. Quail DF, Dannenberg AJ. The obese adipose tissue microenvironment in cancer development and progression. *Nat Rev Endocrinol*. 2019;15:139-154.
41. Jiang X, Shapiro DJ. The immune system and inflammation in breast cancer. *Mol Cell Endocrinol*. 2014;382:673-682.
42. Nicolini A, Carpi A, Rossi G. Cytokines in breast cancer. *Cytokine Growth Factor Rev*. 2006;17:325-337.
43. Johnson L, Mossong J, Dorrington R, et al. International epidemiologic databases to evaluate AIDS southern Africa collaboration life expectancies of south African adults starting antiretroviral treatment: collaborative analysis of cohort studies. *PLoS Med*. 2013;10:e1001418.
44. Bor J, Herbst AJ, Newell M-L, Bärnighausen T. Increases in adult life expectancy in rural South Africa: valuing the scale-up of HIV treatment. *Science*. 2013;339:961-965.
45. Galukande M, Wabinga H, Mirembe F. Breast cancer survival experiences at a tertiary hospital in sub-Saharan Africa: a cohort study. *World J Surg Oncol*. 2015;13:1-8.
46. Gebremariam A, Dereje N, Addissie A, et al. Factors associated with late-stage diagnosis of breast cancer among women in Addis Ababa, Ethiopia. *Breast Cancer Res Treat*. 2021;185:117-124.
47. Islami F, Lortet-Tieulent J, Okello C, et al. Tumor size and stage of breast cancer in Côte D'ivoire and Republic of Congo—results from population-based cancer registries. *Breast*. 2015;24:713-717.
48. Coleman MP, Quaresma M, Berrino F, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol*. 2008;9:730-756.
49. Akuoko CP, Armah E, Sarpong T, Quansah DY, Amankwaa I, Boateng D. Barriers to early presentation and diagnosis of breast cancer among African women living in sub-Saharan Africa. *PLoS One*. 2017;12:e0171024.
50. Joffe M, Ayeni O, Norris SA, et al. Barriers to early presentation of breast cancer among women in Soweto, South Africa. *PLoS One*. 2018;13:e0192071.
51. Dickens C, Joffe M, Jacobson J, et al. Stage at breast cancer diagnosis and distance from diagnostic hospital in a periurban setting: a South African public hospital case series of over 1,000 women. *Int J Cancer*. 2014;135:2173-2182.
52. Donkor A, Lathlean J, Wiafe S, et al. Factors contributing to late presentation of breast cancer in Africa: a systematic literature review. *Arch Med*. 2015;8:1-10.
53. Espina C, McKenzie F, dos-Santos-Silva I. Delayed presentation and diagnosis of breast cancer in African women: a systematic review. *Ann Epidemiol*. 2017;27:659-671.e7.
54. McKenzie F, Zietsman A, Galukande M, et al. Drivers of advanced stage at breast cancer diagnosis in the multicountry African breast cancer-disparities in outcomes (ABC-DO) study. *Int J Cancer*. 2018;142:1568-1579.

## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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