

# Breast Cancer and HIV in Sub-Saharan Africa: A Complex Relationship

## abstract

**Introduction** The number and lifespan of individuals living with HIV have increased significantly with the scale-up of antiretroviral therapy. Furthermore, the incidence of breast cancer in women with HIV is growing, especially in sub-Saharan Africa (SSA). However, the association between HIV infection and breast cancer is not well understood.

**Methods** A literature search was performed to identify articles published in journals pertaining to breast cancer and HIV, with an emphasis on SSA. Selected US-based studies were also identified for comparison.

**Results** Among the 56 studies reviewed, the largest study examined 314 patients with breast cancer and HIV in the United States. There is no consensus on whether HIV infection acts as a pro-oncogenic or anti-oncogenic factor in breast cancer, and it may have no relation to breast cancer. A higher incidence of breast cancer is reported in high-income countries than in SSA, although breast cancer in SSA presents at a younger age and at a more advanced stage. Some studies show that patients with breast cancer and HIV experience worse chemotherapy toxicity than do patients without HIV. Data on treatment outcomes are limited. The largest study showed worse treatment outcomes in patients with HIV, compared with their counterparts without HIV.

**Conclusion** HIV infection has not been associated with different clinical presentation of breast cancer. However, some evidence suggests that concurrent diagnosis of HIV with breast cancer is associated with increased therapy-related toxicity and worse outcomes. Systematic prospective studies are needed to establish whether there is a specific association between breast cancer and HIV.

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## INTRODUCTION

The HIV pandemic remains a public health crisis worldwide. There were 35 million people infected with HIV in 2013, the majority (71%) of whom resided in sub-Saharan Africa (SSA).<sup>1,2</sup> The advent and widespread availability of antiretroviral therapy (ART) has led to both a four-fold decrease in mortality due to AIDS and a three-fold decrease in AIDS-defining cancers (ADCs) worldwide.<sup>3-6</sup> At the same time, as the life expectancy and prevalence of women living with HIV increases, there has been a three-fold increase in the incidence of certain non-AIDS-defining cancers (NADCs), such as lung cancer, Hodgkin lymphoma, squamous cell carcinoma, testicular cancer, and esophageal cancer.<sup>4-6</sup> SSA has experienced similar trends, with a declining incidence of ADCs such as Kaposi sarcoma in Botswana and an increase in NADCs in Tanzania.<sup>7-10</sup>

Breast cancer is the most common cancer among all women in the general population worldwide.<sup>11</sup> Women living in low- and middle-income countries make up 53% of new cancer cases and 62%

of cancer-related mortality globally.<sup>11-13</sup> Among women with HIV worldwide, breast cancer is the most common type of NADC, representing approximately 12% of all new cancer cases and 25% of all cancers.<sup>11</sup> In regions such as SSA, with the prevalence and increased survival of HIV-infected individuals and the increasing incidence of breast cancer, a growing number of women are being affected with both diagnoses. Although the oncologic relationship between HIV/AIDS and certain cancers is well understood, there is little evidence about breast cancer among individuals with HIV infection. The incidence of breast cancer in Africa is estimated to double by 2050, and as such, more information is needed to guide treatment in this unique population of women affected by both HIV and breast cancer.

This review summarizes findings from published studies about the pathogenesis, incidence, clinical presentation, and treatment outcomes of patients with HIV with a concurrent breast cancer diagnosis. Unfortunately, there are numerous inadequacies in data collection, storage, and

analysis systems for studying breast cancer and HIV in SSA. We make recommendations for further interventions and future studies.

## METHODS

We searched the PubMed database up to March 2016. Our primary search strategy combined the following terms with Boolean operators: breast neoplasm; breast malignancy; breast cancer; human immunodeficiency virus; HIV; Africa; SSA; and Africa, south of Sahara. Our search included terms focusing on studies in SSA because of the high burden of HIV and breast cancer in this region, although selected US studies were also included for comparison, because this is where the largest HIV-infected cohorts can be identified. The search was limited to studies performed in humans. As Africa is a trilingual continent, publications were not excluded by language. All publication types were included in this first screen to ensure that no relevant data were missed. All titles and abstracts from each of the searches were examined. The full text of each article was obtained and reviewed if the title or abstract discussed HIV and breast cancer. Articles that discussed HIV and cancer, but not breast cancer, or discussed breast cancer without HIV were excluded.

One reviewer (S.G.) extracted data on publication details (year, authors, study country), study details (study duration, study population), and significant findings. An independent reviewer (N.M.Z.) extracted data from 10% of the articles for external validity; disagreements were discussed, and a consensus was agreed on.

We identified three thematic areas: epidemiologic characteristics (incidence), pathologic characteristics (viral association, genetic association, effects of HIV treatment), and clinical characteristics (clinical presentation, treatment modalities, and outcomes). Results are summarized according to these thematic areas and are presented as global findings—including in the United States, as well as Africa-specific findings. We obtained additional information on global breast cancer incidence, HIV incidence, morbidity, and mortality data from the International Agency for Research on Cancer and Global Health Observatory websites.

A limitation we recognize in this review is the use of the term SSA to refer to all the SSA countries as one group, despite the heterogeneity of the population of the continent in race/genetics and social factors. However, with the limited data on the region, necessity requires that we group them together.

## RESULTS

The initial search yielded 104 titles. After evaluating for relevance, 88 abstracts were selected for further review (Fig 1). The authors reviewed the full text and identified 56 articles that were relevant to the subject matter. This review summarizes breast cancer and HIV/AIDS literature from the selected articles (Data Supplement).

### Incidence of Breast Cancer in Individuals With HIV

Marked variation exists in the reported incidence of breast cancer worldwide—from 95 to 100 cases per 100,000 persons in North America, Northern Europe, and Australia to 13.5 to 30 per 100,000 women in SSA.<sup>11,14,15</sup> Breast cancer is less common in black women than in white women in SSA, with an age-standardized rate of 11.3 per 100,000 in central Africa and 70.2 per 100,000 for white women in South Africa.<sup>16</sup> The breast cancer incidence in Africa continues to increase and is projected to double by 2050.<sup>17-19</sup>

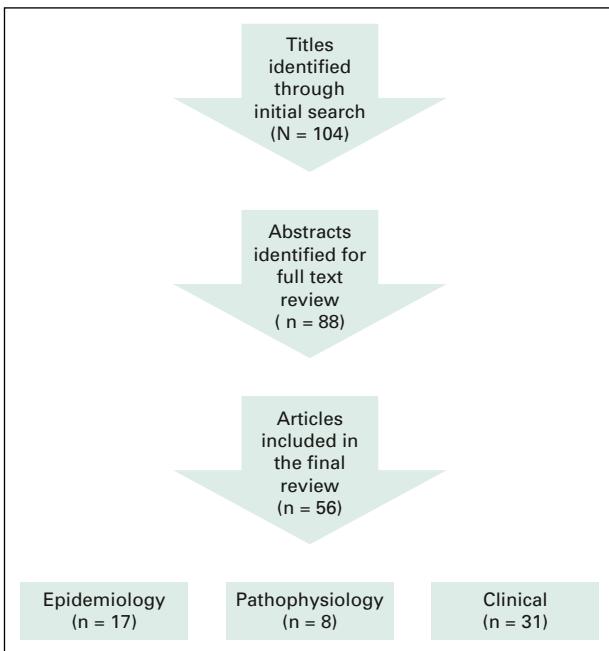
Among patients with HIV, American and European cohorts have shown a drop in standardized incidence ratios of breast cancer in the post-ART era, likely because of greater health care linkage and access to screening through HIV care programs.<sup>20-27</sup> Data from 937 patients in Tanzania also show a significant drop in the incidence of breast cancer in HIV-infected women.<sup>28,29</sup>

### Pathologic Association Between HIV and Breast Cancer

Breast cancer develops as a result of the complex interplay of host, genetic, metabolic, immunologic, and environmental factors, although several malignancies have a well-defined association with viruses (eg, Kaposi sarcoma and human herpesvirus 8).<sup>30</sup> Breast cancer has no established viral (including HIV) associations, although several have been suggested.<sup>31-34</sup>

**HIV and breast cancer molecular pathways and genetic expression.** Evaluation of the genes and molecular pathways involved in HIV infection and breast cancer has revealed that HIV infection and breast cancer might be specifically associated. However, it is disputed whether HIV confers a protective, detrimental, or neutral effect on breast cancer development.

A number of studies have suggested an accelerating or detrimental effect of HIV on breast cancer. Gene-disease association network (GDN) studies have been used to probe the relationship between HIV and breast cancer.<sup>35</sup> In the GDN, two



**Fig 1 –**

Results of systematic search, screening, and data extraction for review of breast cancer and HIV.

disorders are interrelated if they share at least one common gene mutation. Microarray data revealed that HIV infection and breast cancer share 17 genes, of which 10 are overexpressed and seven are underexpressed in both diseases.<sup>36</sup> Other studies have demonstrated similar genetics, signaling pathways, proteins, and receptors common to both HIV and breast cancer.<sup>35,37</sup> The common expression of genes and receptors indicates possible ways in which HIV might directly modify the natural history of breast cancer, but does not establish a causative link. However, there is evidence that HIV infection promotes tumor growth via immune signaling, angiogenesis, and metastasis in breast cancer.<sup>36,38-48</sup> These findings may provide the causative link between breast cancer and HIV.

In contrast, a few studies suggest a protective effect of HIV on breast cancer. HIV infection activates cell death pathways, which may lead to the decreased cancer burden in these patients.<sup>49</sup> In addition, an in vitro study suggests that HIV replication in human breast cells hinders their growth by affecting growth factor receptors, suggesting that HIV infection may counteract oncogenesis in breast cancer cells.<sup>50</sup>

**HIV-associated comorbidities and breast cancer.** Finally, there are studies suggesting development of breast cancer in patients with HIV through comorbidities, such as metabolic syndrome due to ART<sup>35,51,52</sup> associated with HIV and HIV-related therapy. Several breast cancer risk factors are associated with metabolic syndrome, such as

abdominal obesity, high blood glucose level, high blood pressure, high triglyceride levels, and low high-density lipoprotein levels.<sup>52</sup> HIV infection and ART are known to be associated with a variety of metabolic changes and disorders, including metabolic syndrome. Several published studies found an overall increase in the incidence of metabolic syndrome in patients with HIV receiving ART over time,<sup>51</sup> making this comorbidity particularly relevant for patients with HIV and breast cancer.

### Clinical Characteristics

**Presentation.** On the basis of most series available, the median age at diagnosis for patients with breast cancer without HIV in high-income populations is 61 years, compared with 10 to 15 years younger in patients with HIV.<sup>53-60</sup> However, Shiels et al<sup>61</sup> reported that in their cohort of 110 US patients, age at breast cancer diagnosis was similar in the AIDS and general populations. In high-income countries, there is controversy regarding the effect of HIV on age at presentation. Patients with breast cancer in SSA generally present at a relatively younger age regardless of HIV status.<sup>62-64</sup> The overall mean age of presentation in West African women is between 35 and 45 years, 10 to 15 years earlier than women in high-income countries.<sup>14,65,66</sup> Similarly, a 3-year retrospective review of 374 patients with breast cancer in Kenya showed a median age of 44 years,<sup>64,67-69</sup> and the mean age in a Tanzanian cancer registry is 44.7 years.<sup>28</sup> A 2-year study at the Tygerberg Academic Hospital in Cape Town, South Africa, reported trends similar to the population in the high-income countries, with a median age at presentation of 56 years for patients without HIV compared with 42 years for patients with HIV ( $P < .001$ ).<sup>70</sup>

Patients with breast cancer in high-income countries predominantly present with early-stage disease. Patients with HIV and breast cancer in the United States present with stage distribution similar to their seronegative counterparts<sup>57,71-73</sup>: 60% of all patients present with stage I disease, 33% with stage II or III disease, and 5% with stage IV disease.<sup>74</sup> In addition, the distribution of histologic subtypes of breast cancers was found to be independent of HIV status.<sup>75,76</sup> However, few case reports of patients with HIV and breast cancer have noted a more disseminated breast cancer and marked aggressiveness despite favorable biologic prognostic parameters.<sup>55,56,77,78</sup>

In SSA, a majority of patients present with advanced-stage disease, with 89.6% and 72.8% of patients with breast cancer in Kenya and Nigeria, respectively,

presenting with advanced-stage disease.<sup>67,68</sup> A study by Vorobiof et al<sup>16</sup> showed that black female patients in South Africa presented with advanced-stage disease (77.7%) at a higher rate than white female patients (30.7%). Table 1 lists the data for clinical presentation in the studies reviewed.<sup>3,67,68,70</sup>

Molecular subtypes of breast cancer tumors in patients with HIV infection are similar to those of geographically matched patients with breast cancer without HIV in high-income countries and SSA. The University of Maryland cohort of US patients with breast cancer had primarily estrogen receptor– and progesterone receptor–positive disease (72% and 61%, respectively), which was similar in patients with HIV, except for human epidermal growth factor receptor 2 overexpression, which was higher in the HIV subset.<sup>57</sup> Similarly, among South African patients, approximately two thirds of breast tumors

were hormone receptor–positive regardless of HIV status.<sup>3,70,79</sup>

Studies examining the effect of HIV-related immunosuppression on the risk of breast cancer in patients with HIV are scant. Some suggest that patients with HIV may develop breast cancer due to impaired immune surveillance,<sup>80,81</sup> although a few small studies have shown no relationship between immunosuppression and breast cancer.<sup>82-84</sup> In the University of Maryland study, the median CD4 count was 437.5 cells/ $\mu$ L.<sup>57</sup> Similarly, a median CD4 count of 424 cells/ $\mu$ L was noted in an Italian cohort,<sup>59</sup> and 50% of South African patients with breast cancer and HIV had CD4 counts between 200 and 499 cells/ $\mu$ L.<sup>3</sup> A case report by García-Tejedor et al<sup>85</sup> of a patient with HIV and hepatitis C virus infection even documented a CD4 count as low as 181 cells/mL. CD4 count was not associated with

**Table 1** – Demographic and Clinical Characteristics of Patients With Breast Cancer for Studies Included in the Review of Breast Cancer and HIV (presented by study)

Study	Country	No. of Patients with Breast Cancer	No. of Patients with HIV and Breast Cancer (%)	Patients With Advanced-Stage Breast Cancer, %	Median Age at Diagnosis, years	Median Age at Diagnosis of Patients With HIV, years	Receptor Status in Patients Without HIV, %	Receptor Status in Patients With HIV, %	Differences in Receptors on the Basis of HIV Status
Hurley et al <sup>72</sup>	US	20	20 (100)	10	44				
El-Rayes et al <sup>73</sup>	US	38	38 (100)	20					
Singh et al <sup>57</sup>	US	18	18 (100)	28	48		ER: 72 PR: 61 HER2: 44 TNBC: 17		Higher incidence of HER2-positive status in patients with HIV
Othieno-Abinya et al <sup>67</sup>	Kenya	250	0 (0)	89.6	44				
Ikpat <sup>66</sup>	Nigeria	300	0 (0)		42.7				
Adebamowo and Adekunle <sup>68</sup>	Nigeria	250	0 (0)	72.8	43				
Anyanwu <sup>62</sup>	Nigeria	179	0 (0)	72	46.9				
Cubasch et al <sup>3</sup>	Soweto, South Africa	1,092	765 (70)	50		ER: 58 PR: 47 HER2: 22 TNBC: 19	ER: 62 PR: 52 HER2: 27 TNBC: 16		No difference
Langenhoven et al <sup>70</sup>	Cape Town, South Africa	586	31 (5)	55	56	42	ER: 64 PR: 51 HER2: 36 TNBC: 16	ER: 52 PR: 29 HER2: 32 TNBC: 16	No difference
Amir et al <sup>28</sup>	Tanzania	937	0 (0)		44.7				

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; TNBC, triple-negative breast cancer.

breast cancer stage at presentation, subtype, or tumor grade in these studies.

In summary, the average age of breast cancer diagnosis is lower in SSA women, compared with their counterparts in high-income countries. Although findings from cohorts in high-income countries suggest an earlier age at diagnosis for patients with HIV and breast cancer compared with those without HIV, those studies were generally small and inconclusive.<sup>57</sup> Cancer stage at presentation for patients with breast cancer in the United States is similar in patients both with and without HIV.<sup>57,71</sup> In SSA, age and stage at presentation of patients with and without HIV and with breast cancer were similar.<sup>79</sup> Table 1 lists the data for clinical presentation in the studies reviewed.<sup>3,67,68,70</sup>

**Treatment and tolerability.** Suneja et al<sup>86</sup> analyzed registry data from three US states (Connecticut, Michigan, and Texas) involved in the linkage of cancer and HIV/AIDS registries from 1996 to 2010. They identified 3,045 adults with concurrent HIV infections and cancer diagnoses, of whom 108 had HIV and breast cancer. Their results showed that for most cancers, a significantly higher proportion of individuals with HIV did not receive cancer treatment. However, in the subset of patients with HIV and breast cancer, there was no statistically significant difference in receipt of standard therapy for both local and advanced breast cancer compared with matched patients without HIV. The percentage of patients without treatment was 9% and 4.7% in patients with and without HIV, respectively. The results were the same in the pre-ART and ART era.<sup>86</sup> The major limitations for the study were missing data regarding some prognostic indicators for therapy, as well as details on treatment, with first course of treatment defined as any treatment commenced within 6 months of the initial diagnosis.<sup>86</sup>

In patients with HIV receiving ART and chemotherapy, studies in high-income countries have shown that potential treatment interactions may result in worse adverse events in patients with HIV receiving chemotherapy compared with their seronegative counterparts.<sup>87</sup> Hurley et al<sup>72</sup> published a retrospective review on 20 patients with HIV and breast cancer in Florida and found that chemotherapy was poorly tolerated in patients with HIV; grade 3 and 4 myelosuppression was seen in five of the seven patients treated with anthracycline-based chemotherapy. In that study, two patients who completed adjuvant therapy then progressed to advanced AIDS. In contrast, patients who received

surgery and hormonal therapy alone experienced fewer adverse events compared with patients who received chemotherapy.<sup>72</sup> Similarly, El-Rayes et al<sup>73</sup> showed in a series of five premenopausal women in Michigan that receipt of chemotherapy was complicated by neutropenia in four of the five patients who received chemotherapy. The rate of neutropenia and neutropenic fever in patients without HIV was reported to be 3% to 15%.<sup>88</sup> The authors also found progression to AIDS in two of 38 patients, with a notable increase in viral load or decrease in CD4 count despite concurrently receiving ART with chemotherapy.<sup>73</sup> This trend was also observed in a retrospective study in Maryland by Singh et al<sup>57</sup> evaluating data on 18 patients with ductal carcinoma in situ or breast cancer and HIV/AIDS. They found grade 2 and 3 infectious toxicity in 50% of patients and 70% of those requiring treatment delays and dose reduction in chemotherapy<sup>57</sup>; only 60% of patients with HIV and breast cancer overall completed chemotherapy. Parameswaran et al<sup>89</sup> similarly reported that 56% of patients with HIV and breast cancer in New York required treatment delays and dose reduction in chemotherapy, compared with 30% of patients without HIV. Although CD4 count in patients with HIV is not shown to be associated with age and stage at presentation, some have speculated that CD4 count at diagnosis may dictate chemotherapy tolerance.<sup>90</sup>

In contrast, Langenhoven et al<sup>70</sup> reported that in a South African cohort, more than 84% of patients with breast cancer, including 19 patients with HIV and breast cancer, who initiated systemic chemotherapy completed it without serious toxicity, regardless of HIV status. This was found despite a mean decline in CD4 count during chemotherapy, from 477 cells/ $\mu$ L to 333 cells/ $\mu$ L. There was no statistically significant difference in hematologic toxicity requiring dose modification. However, grade 3 or 4 lymphocytopenia developed only in the patients with HIV (26.4%;  $P = .001$ ). The study did not report baseline lymphocyte count for patients with HIV versus those without HIV before initiating systemic therapy. In addition, of 19 patients with HIV and breast cancer included in the toxicity analysis, there were no data on how many patients were receiving ART concurrently with chemotherapy or details of the ART regimen.<sup>70</sup> Toxicities associated with chemotherapy are listed by study in Table 2.

There are limited studies examining treatment outcomes with surgery and radiation therapy in patients with HIV/AIDS and breast cancer. Hurley et al<sup>72</sup> noted that patients with HIV who received breast surgery without chemotherapy

**Table 2** – Chemotherapy Toxicity Characteristics in the Studies Included in the Review of Breast Cancer and HIV (presented by study)

Study	Total No. of Patients With Breast Cancer	No. of Patients Receiving Chemotherapy	Patients With Grade 3 Hematologic Toxicity, %	Patients With Grade 2 & 3 Infectious Toxicity, %	Patients Who Completed Chemotherapy, %	Patients Receiving Chemotherapy Requiring Treatment Delays or Dose Reductions, %	No. of Patients Whose Disease Progressed to Advanced AIDS	Patients Developing Grade 3 or 4 Myelosuppression, %
Singh et al <sup>57</sup>	18	10	40	50	60	70		
Langenoven et al <sup>70</sup>	31	19						26.4 (lymphocytopenia)
Hurley et al <sup>72</sup>	20	7					2	71.4
El-Rayes et al <sup>73</sup>	5	5						80 (neutropenia)

experienced fewer adverse events. Buehrer et al<sup>91</sup> found that surgical management was not associated with complications in patients with HIV in North Carolina. Radiotherapy seems to be well tolerated on the basis of a case report of this subpopulation.<sup>75</sup> However, rigorous data are lacking in this area.

Overall, these findings suggest that HIV/AIDS may negatively affect chemotherapy tolerability with a greater degree of immunosuppression observed with concurrent ART, in particular, zidovudine and protease inhibitors. This in turn may reduce treatment efficacy and treatment adequacy through poor adherence, dose adjustments, treatment delays, and/or early discontinuation of therapy.<sup>73,89,92</sup>

**Outcomes.** The largest study evaluating survival in patients with HIV and cancer used data from six US states participating in a linkage of cancer and HIV/AIDS registries and had a total of 1,816,461 patients with cancer, including 6,459 (0.36%) with HIV.<sup>93</sup> Cancer diagnosis was limited to adults with 14 common ADCs and NADCs occurring between 1996 and 2010. A total of 314 patients with HIV and breast cancer were identified. The authors reported that patients with HIV and NADCs are more likely to die as a result of their cancer than patients without HIV. This was independent of cancer stage or receipt of cancer treatment. Specifically for breast cancer, the hazard ratio was 4.62 (95% CI, 3.92 to 5.45) for all-cause mortality and 2.61 (95% CI, 2.06 to 3.31) for breast cancer-specific mortality. ART treatment in the people living with HIV was not reported; however, cancer-specific mortality limited to the ART era was 3.43 (95% CI, 2.35 to 5.01) for people living with HIV and breast cancer. This investigation is the largest systematic review of survival within this subpopulation, but its limitations include incomplete data on HIV viremia and measures of immunosuppression.<sup>93</sup>

Small studies in SSA have not shown a difference in breast cancer outcomes when comparing patients with HIV with those without HIV. Coghill et al<sup>94</sup> conducted a retrospective study using the Kampala cancer registry. Among those with HIV infection (24 of 220; 10.9%), they found a more than two-fold increased risk of death within 1 year of a breast cancer diagnosis compared with individuals without HIV. The data for breast cancer alone did not show a significant difference in the hazard ratio for 1-year survival. This study was limited by the small population of patients with HIV and breast cancer, which may have affected the ability to achieve a statistically significant difference in survival within this group. Other limitations include incomplete data on cancer stage at presentation, treatment, and degree of immunosuppression.<sup>94</sup>

In contrast, Gotti et al<sup>95</sup> noted an improvement in overall survival in ADCs compared with NADCs in the ART era in the United States. The overall median survival was 1.6 years for NADCs and 3.4 years for ADCs. Specifically in patients with breast cancer, considered an NADC, no significant association was noted between HIV clinical variables (ie, combination antiretroviral therapy, CD4, viral load) and risk of mortality.<sup>95</sup> These findings suggest that patients with HIV and breast cancer may have an increased risk of cancer-specific mortality compared with patients without HIV, although these studies had many limitations.

In conclusion, the prolonged survival and increasing prevalence of HIV among women globally in conjunction with the increasing burden of breast cancer worldwide has led to an emerging and poorly understood subpopulation of patients with HIV and breast cancer. Although this increased life expectancy for patients with HIV has led to many other NADCs to be described, there are limited data on the relationship between HIV and breast cancer.

The natural history of breast cancer in individuals with HIV is poorly understood, and it is unknown whether viral infection is a protective factor for breast cancer development or a risk factor for accelerated oncogenesis. A definitive link between these two disease processes remains to be established. Presentation of breast cancer in patients with HIV in SSA has age and stage distribution, as well as molecular subtypes, similar to that in high-income countries.<sup>79</sup> Data from high-income countries' cohorts suggest an earlier age at diagnosis in patients with HIV and breast cancer compared with their counterparts without HIV in several small inconclusive investigations.<sup>57,59</sup>

The largest series to investigate cancer outcomes was a retrospective analysis of registry data from the United States.<sup>93</sup> Although the results provide more insight into outcomes among patients with breast cancer and HIV infection, follow-up and treatment data were missing for a significant number of patients in this cohort. Similarly, many of the studies in SSA

had poor data collection, storage, and analysis systems. Larger prospective multicenter and cross-border cohort studies of patients with HIV in SSA, especially in those countries that have a high HIV disease burden, are needed to establish the true prevalence and incidence of concurrent breast cancer and HIV infection and to identify interactions between these diseases. The impact of immunobiology on outcomes also deserves further exploration. In addition, screening, diagnosis, access to uninterrupted treatments, palliative care services, and rehabilitation of patients who have survived HIV and breast cancer are other aspects of health delivery systems in the SSA countries that warrant further attention and study. Such information can help to guide the design of safe treatment algorithms for patients with HIV and breast cancer to achieve improved outcomes in this important and emerging population in our global community.

DOI: 10.1200/JGO.2016.006585

Published online on ascopubs.org/journal/jgo on January 11, 2017.

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The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to [www.asco.org/rwc](http://www.asco.org/rwc) or [ascopubs.org/jco/site/ifc](http://ascopubs.org/jco/site/ifc).

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No relationship to disclose

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No relationship to disclose

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No relationship to disclose

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