after HCV treatment in this population. Moreover, VLWH taking NRTIs had a significant increase in LDL. Therefore, more research is needed in VLWH with HCV co-infection and advanced liver fibrosis to identify whether lower thresholds for initiating statin therapy post-SVR are warranted to reduce CVD risk. Overall, these findings have important implications for clinicians who care for VLWH.

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Conflicts of interest

There are no conflicts of interest.

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OPEN

Impact of efavirenz on hormone-positive breast cancer survival in women living with HIV

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Women living with HIV and breast cancer have poorer survival than HIV-negative women. Efavirenz–estrogen interactions are documented; however, the survival impact is unknown. Survival between women with estrogen-receptor positive breast cancer taking efavirenz ($n = 38$) and nonefavirenz regimens ($n = 51$) were compared. The 5-year overall-survival was 48.9% [95% confidence interval (CI) 33.0–72.2 and 51.1% (95% CI 34.0–76.8)] in the efavirenz and nonefavirenz groups, respectively suggesting efavirenz is unlikely driving poorer survival in women living with HIV and estrogen-receptor positive breast cancer.

Introduction

Women living with HIV (WLWH) diagnosed with estrogen-receptor positive (ER+) breast cancer are at

increased risk of dying compared with HIV-negative women [1,2]. The reasons for this are unknown but one area that has not been well explored is the effect of antiretroviral therapy (ART) on ER+ breast cancer survival.

Efavirenz (EFV), although no longer first-line treatment for HIV, is still used throughout sub-Saharan Africa (SSA) [3]. Interactions between EFV and estrogen have been documented [4]. Clinically, gynecomastia development in children and men taking EFV have been noted [5–8] which is thought to be due to EFV-induced estrogen receptor activation, as demonstrated through in-vitro studies [9,10]. No studies, however, have been conducted evaluating the in-vivo effects of EFV in hormone-dependent malignancies, including breast cancer.

The aim of this study is to retrospectively evaluate if EFV containing ART regimens impacts survival in WLWH and ER+ breast cancer.

Methods

Female patients, at least 18 years of age, with ER+ (luminal A) breast cancer and living with HIV were retrospectively identified from the Thabatse cancer cohort (TCC). Since 2010, this cohort has consecutively captured clinical and demographic data on approximately 65% of cancers in Botswana [11]. Patients were enrolled from the four principal oncology treatment facilities throughout Botswana. A baseline interview was conducted at enrollment and participants were followed quarterly for 5 years. WLWH were enrolled from the same treatment facilities as HIV-negative women. Breast cancer stage was calculated based on the American Joint Committee on Cancer (AJCC) seventh edition based on clinical, radiographic, and pathological results available in the TCC [12]. Tumor receptor status was determined based on immunohistochemical analysis and only patients with luminal A molecular subtype (ER+, PR+/−, Her2−) were included in the analysis. HIV test results and ART regimens were collected from the patient's medical records.

The primary outcome variable was overall survival (OS) defined from the date of breast cancer diagnosis to the date of death or administrative censoring (5 years following enrollment in the cohort). Vital status was determined during quarterly follow-up calls.

Categorical and continuous variables were compared by EFV vs. non-EFV containing ART regimens using chi-squared, Fisher's exact, and Student's *t*-tests wherever appropriate. Kaplan–Meier survival curves stratified by EFV status were created. Unadjusted and adjusted cox proportional hazard regression models were constructed to assess the effect of OS between the two groups. Statistical analyses were completed using R-Studio [13].

Results

A total of 112 patients were identified living with HIV and ER+ breast cancer. Due to unknown HIV regimen, 23 patients were excluded. Of the remaining women, 38 were taking EFV-containing and 51 were taking non-EFV-containing regimens (Supplemental Figure 1, http://links.lww.com/QAD/D199).

No significant differences were noted between the groups except that a significantly higher proportion of patients in the EFV group were enrolled between 2013 and 2016 compared with the non-EFV group (45 vs. 22%, $P = 0.002$). Most breast cancer patients, in both groups, were diagnosed with advanced disease (≥stage 3). There was no significant difference in treatments received between the groups. The EFV group had a higher proportion of women with $CD4^+$ counts less than 500 cells/μl compared with the non-EFV group (68 vs. 29%, $P = 0.003$) (Supplement Table 1, http://links.lww.com/QAD/D200).

The 5-year OS was 48.9% (95% CI 33.0–72.2) and 51.1% (95% CI 34.0–76.8) in both the EFV and non-EFV groups, respectively. There was no significant EFV survival effect noted in the unadjusted model (hazard ratio 1.05, 95% Cl 0.46–2.3). The model was then adjusted for $CD4^+$ count which remained nonsignificant (hazard ratio 0.98, 95% CI 0.4–2.3) (Fig. 1). Post hoc subgroup analyses were completed evaluating only early-stage (≤ stage 2) breast cancer and including both luminal A and B patients; however, neither analysis demonstrated a significant survival difference between EFV and non-EFV groups (data not shown).

Discussion

In this exploratory analysis, we compared the survival of WLWH and ER+ breast cancer taking EFV vs. non-EFV ART regimens. No significant EFV survival effect was noted between the two groups. However, irrespective of EFV use, OS in this cohort was poor. This poor survival was likely due to the high number of women who presented with late-stage disease.

HIV's effect on breast cancer survival is mitigated in advanced stage disease. Previous studies have found that WLWH diagnosed with stage 1–3 breast cancer had worse survival than HIV-negative women; however, no survival differences were noted between WLWH or HIV-negative women with stage 4 breast cancer [1,2]. In this current study, sub-group analysis of stage 1 and 2 breast cancer only demonstrated decreased 5-year survival in the EFV vs. non-EFV groups (55 and 83%, respectively). These groups, however, were underpowered and so did not reach statistical significance. This suggests that any negative effect on breast cancer survival conferred by EFV is likely

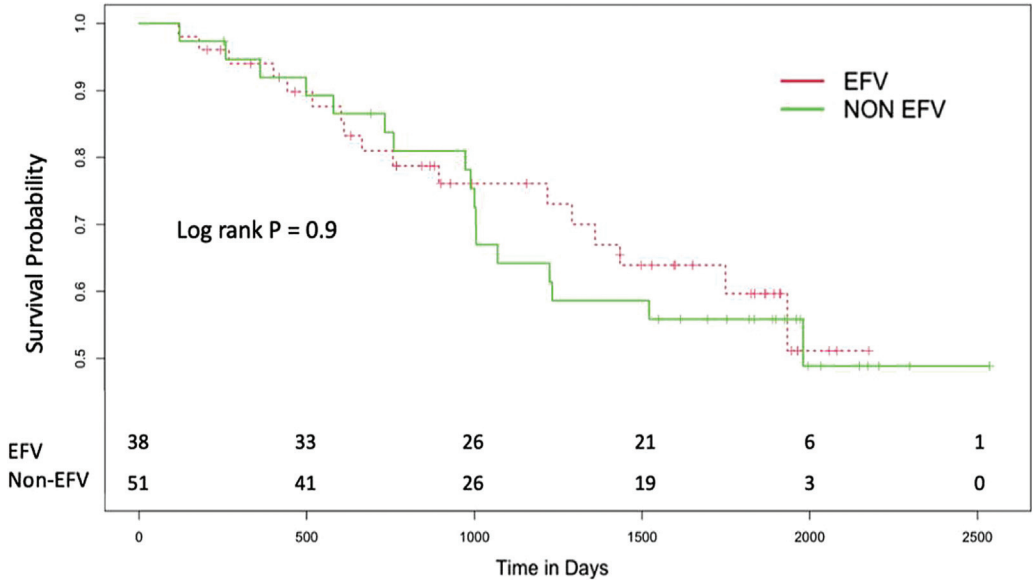

Fig. 1. Overall survival in women living with HIV and estrogen receptor + breast cancer stratified by efavirenz vs. non-efavirenz containing antiretroviral therapy regimens.

small and in this cohort, may be masked by the large proportion of patients with late-stage disease.

There are several strengths of this current study. Previous studies have evaluated the effect of HIV on breast cancer; however, to our knowledge, this is the first study to evaluate the effect of specific ART treatment regimens on breast cancer survival. Additionally, this study was able to capture and longitudinally follow most women with ER+ breast cancer in Botswana. This study was limited in several respects. Despite involving approximately 65% of WLWH and ER+ breast cancer in Botswana, the sample size remained small decreasing the precision of the results. Additionally, data was limited regarding if women switched ART regimens during the data collection period, especially given the post-2016 recommendation that women switch from EFV to non-EFV ART regimens [14]. Lastly, the dataset did not capture information on adjuvant endocrine therapy use, such as Tamoxifen.

In conclusion, no statistically significant survival difference was seen between WLWH and ER+ breast cancer taking EFV vs. non-EFV-containing ART regimens and as such, our data cannot conclude that EFV is the driving factor underlying the poorer survival compared with HIV-negative women with ER+ breast cancer. Further studies, with additional power, are needed to investigate the causes of this survival difference more fully.

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Conflicts of interest

There are no conflicts of interest.

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Safety of tenofovir alafenamide in people with HIV who experienced proximal renal tubulopathy on tenofovir disoproxil

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Twenty-eight individuals who experienced proximal renal tubulopathy (PRT, Fanconi syndrome) while receiving tenofovir disoproxil initiated tenofovir alafenamide (TAF) and were followed for 5 years. None developed recurrent PRT or experienced significant changes in estimated glomerular filtration rate (by creatinine or cystatin-C), albuminuria, proteinuria, retinol-binding proteinuria, fractional excretion of phosphate, alkaline phosphatase, or bone mineral density at the lumbar spine. These data suggest that TAF is a well tolerated treatment option for individuals vulnerable to developing PRT.

Tenofovir disoproxil (TDF) is among the most widely used antiretroviral therapy (ART) with potent activity against HIV and hepatitis B. The relatively high systemic and renal tubular tenofovir exposures obtained with TDF may affect mitochondrial function in the renal tubules [1,2], resulting in estimated glomerular filtration rate (eGFR) decline and proteinuria [3,4]. If unrecognized, continued exposure to TDF may result in acute tubular injury and proximal renal tubulopathy (PRT, Fanconi syndrome), which is characterized by phosphate and glucose wasting as a result of reduced reabsorption of these solutes from the glomerular ultrafiltrate [1,5,6].

Tenofovir alafenamide (TAF) is also a tenofovir prodrug, however, compared to TDF has approximately 90% lower plasma tenofovir exposure. TAF has been extensively evaluated in clinical trials, with consistently lesser effects on renal biomarkers, and no reported cases of PRT [7,8]. TAF was shown to be a suitable treatment option for individuals with mild-moderate renal impairment [9] or eGFR decline [10] on TDF, and case reports have suggested that TAF may potentially be an option for people who experienced treatment-limiting PRT on TDF [11–13]. In 2018, we initiated a study to examine the safety of TAF in a larger cohort of individuals who experienced treatment-limiting PRT on TDF. We previously reported 12 and 96-week safety data [14,15], and here present the final study results after 5 years of follow up.

Adults with HIV, a history of TDF-associated PRT (defined as $\geq$2 of normoglycemic glycosuria [$\geq$1+ on dipstick]; proteinuria [$\geq$1+ on dipstick or urine protein/creatinine ratio >30 mg/mmol]; hypophosphatemia [serum phosphate $\leq$0.64 mmol/l); rapid eGFR decline [>5 ml/min/1.73 m^2/year with >25% reduction from baseline], or a renal biopsy showing acute tubular injury not explained by other causes, with clinical resolution of these abnormalities following TDF discontinuation) and HIV RNA less than 200 copies/ml were switched to TAF-based ART and followed up for 5 years. In the present analyses, we evaluated the incidence of recurrent PRT, adverse events affecting kidneys and bone, reasons for TAF discontinuation, and changes in annual measurements of eGFR (by creatinine and by cystatin-C) [16], urine albumin/creatinine, protein/creatinine, retinol-binding protein/creatinine, and fractional excretion of phosphate using multilevel mixed effects linear regression models. We also evaluated changes in annual measurements of alkaline phosphatase and bone mineral density (BMD, by dual X-ray absorptiometry) at the lumbar spine and total hip at baseline, years 1, 2, and 5. All participants provided written informed consent. The trial was registered under EudraCT 2016-003345-29.