

THE LANCET HIV

Supplementary appendix

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

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

Appendix

Supplementary List 1: List of ethics approval

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

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

Author (Year)	Country (region)	Study design (study years)	Eligibility criteria	HIV exposure assessment	No. of HIV+ / HIV- BC women	Outcome(s)	HR for effect of HIV (95% CI)	Comments
Sub-Saharan Africa (SSA)								
Coghill et al (2013)(1)	Uganda	Retrospective cohort (population-based 2003-2010) – based on Kampala Cancer Registry Database and medical records at Uganda Cancer Institute and Mulago Hospital	Adults aged at least 18 years at diagnosis of common cancers including breast cancer	HIV ascertained based on documented positive HIV antibody test, medical history of HIV infection and an HIV clinic referral letter	24 / 196	All-cause mortality at 1 year following cancer diagnosis	(HR adjusted for age, year of cancer diagnosis and stage at diagnosis) 2.04 (0.76-5.47)	40% LTFU within 1 year of follow-up. Slightly better survival in more recent years- may be due to availability of ART or improvements in cancer diagnosis and treatment
Cubasch et al (2018)(2)	South Africa	Retrospective cohort (2009-2014)- based on ambient data at the Chris Baragwanath Academic Hospital (CHBAH)	Incident breast cancer women diagnosed at CHBAH	HIV testing was done	88 / 411	All-cause mortality at 4 years following breast cancer diagnosis	(HR adjusted for age, stage, grade and receptor subtype) 1.39 (0.83-2.33)	48% LTFU at end of 4 years of follow-up Outcome (death of any cause) also included terminally-ill patients defined as patients unlikely to survive more than 3 months
Sadigh et al (2019)(3)	Botswana	Prospective cohort (2010-2018) based on data from the Thabotse Cancer Cohort – 4 oncology centres in Botswana	Women aged at least 18 years and with known HIV status	Not clearly specified	151 / 327	All-cause mortality at 5 years following breast cancer diagnosis	(HR adjusted for age, cancer stage, receptor subtype and income) 1.82 (1.32-2.49)	Conference abstract only Incomplete data on cancer stage, treatment and tumour receptor subtypes 1.5% LTFU at 5years
Brandao et al (2019)(4)	Mozambique	Prospective cohort (hospital-based -2015-2017)	Women diagnosed with breast cancer at Maputo Central Hospital	Not clearly specified	52 / 152	All-cause mortality within 2 years of follow-up	(Unadjusted HR) 1.52 (0.92-2.51)	Conference abstract only LTFU not reported
McCormack et al (2020)(5)	Namibia, South Africa, Zambia, Uganda and Nigeria	Prospective cohort (hospital-based 2014- to date)	Women aged at least 18 years with incident breast cancer	Self-reported HIV status	315 / 1841	All-cause mortality at 3 years following breast cancer diagnosis	(HR adjusted for age, stage and tumour grade) 1.48 (1.22-1.81)	Very low LTFU (5%) Women with unknown HIV status were classified as being HIV-negative
North America								
Biggar et al (2005)(6)	USA (New York state)	Population-based cohort study (record linkage of cancer registry & HIV/AIDS registry records) (1980-2000)	Adults aged 15-69 yrs. at AIDS diagnosis and subsequently diagnosed with cancer	AIDS status as identified through linkage to the HIV/AIDS registry	67 / 15225	All-cause mortality within 2 years of the cancer diagnosis	(HRs adjusted for age, race, and calendar time of cancer onset) In 1990-1995: 5.4 (3.8-7.8);	Better survival in 1996-2000 when effective ART became available. The non-AIDS group included HIV+ individuals who never developed AIDS

							In 1996-2000: 1.6 (0.7-3.8)	
Coghill et al (2015)(7)	USA (six states: Colorado, Connecticut, Georgia, Michigan, New Jersey and Texas)	Retrospective population-based cohort study – the HIV/AIDS Cancer Match study, a record linkage of several population-based registries (1996-2014)	Individuals diagnosed with 14 common invasive cancers during the HAART era (i.e. from 1996 to 2007-2010 depending on registry) with follow-up to the end of 2014	HIV status as identified through linkage to population-based HIV/AIDS registries	314 / 386041	(i) Cancer-specific mortality (ii) All-cause mortality	(HRs adjusted for race and age, year and tumour stage at cancer diagnosis) For (i): All stages: 2.61 (2.06-3.31) Localised/regional: 2.61 (1.96, 3.41) For (ii): All stages: 4.62 (3.92-5.45) Localised/regional: NR	From 1996 onwards both HIV and AIDS were reportable conditions in the USA. Further adjustment for receipt of any first-course treatment (i.e. surgery, chemotherapy, radiotherapy, hormonal therapy) did not affect the magnitude of the estimated HIV effect on breast cancer-specific survival.
Coghill et al (2019a)(8) Cancer	USA	National Cancer Database – nationwide hospital-based registry. Retrospective cohort based on the National Cancer Database, a nationwide hospital-based registry (2004-2014)	Patients diagnosed with selected cancer types, including female breast cancer, between 2004 and 2012, and followed-up to the end of 2014	HIV status clinically ascertained at the time of the cancer diagnosis.	Stages I-III only: 957 / 1,099,101 Stages I-IV: 1084 / 1,158,865	All-cause mortality	(HRs adj. for age, race, calendar year, household income, health insurance & cancer facility) <u>Stages I-III only:</u> 1.85 (1.68-2.04) <u>Stages I-IV:</u> 1.77 (1.62, 1.94)	HIV+ women had more advanced stage at BC diagnosis.
Coghill et al (2019b)(9) JAMA Oncol	USA	Retrospective population-based cohort assembled through record linkage of SEER and Medicare databases (1996-2014)	Patients aged ≥65 yrs. diagnosed with a single local or regional stage cancer who received appropriate treatment within the first year after cancer diagnosis and who survived at least 1 yr. after cancer diagnosis	HIV/AIDS diagnoses ascertained from Medicare claims	50 / 96124	(i) All-cause mortality (ii) Cancer-specific mortality	(HR adjusted for race, income, age, calendar year, stage at diagnosis and treatment) (i) 1.85 (0.96-3.55) (ii) 1.50 (1.01-2.24)	
Chhatre et al (2019)(10)	USA	Retrospective population-based cohort based on record linkage between SEER and Medicare databases (2003-2013)	Fee-for-service Medicare enrollees diagnosed with a primary breast cancer between 2000-2011 followed up to the end of 2013.	HIV/AIDS diagnoses ascertained from Medicare claims (physician, outpatient and inpatient claims)	176 / 163904	(i) All-cause mortality (ii) Breast cancer specific mortality	(HR adjusted for age, year at diagnosis, race, marital status, comorbidity, SE variables, tumour stage and treatment) (i) 2.99 (2.61-3.43) (ii) 2.84 (2.29, 3.52)	

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

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

	Crude HIV effect		Model A ^α		Model B ^β		Model C ^γ	
	Deaths/Total	HR (95%CI)	Deaths/Total	HR (95%CI)	Deaths/Total	HR (95%CI)	Deaths/Total	HR (95%CI)
All women								
HIV-	432/1184	1.00	432/1184	1.00	430/1179	1.00	232/717	1.00
HIV+	137/313	1.35 (1.11-1.63)	137/313	1.52 (1.24-1.87)	136/312	1.46 (1.19-1.79)	84/212	1.47 (1.12-1.93)
All women if alive beyond 18 months								
HIV-	163/821	1.00	163/821	1.00	163/818	1.00	91/513	1.00
HIV+	50/196	1.40 (1.02-1.93)	50/196	1.54 (1.10-2.16)	50/196	1.49 (1.06-2.10)	34/138	1.58 (1.03-2.44)
All non-metastatic women								
HIV-	285/965	1.00	285/965	1.00	284/961	1.00	149/606	1.00
HIV+	98/255	1.48 (1.18-1.87)	98/255	1.64 (1.29-2.09)	97/254	1.56 (1.22-1.99)	66/184	1.71 (1.25-2.34)
Non-metastatic women alive beyond 18 months								
HIV-	130/727	1.00	130/727	1.00	130/724	1.00	70/467	1.00
HIV+	41/172	1.49 (1.04-2.12)	41/172	1.58 (1.09-2.28)	41/172	1.52 (1.04-2.20)	29/127	1.66 (1.04-2.64)
All metastatic women								
HIV-	136/171	1.00	136/171	1.00	135/170	1.00	83/108	1.00
HIV+	28/39	0.95 (0.63-1.45)	28/39	1.10 (0.70-1.73)	28/39	1.07 (0.67-1.70)	18/28	0.98 (0.54-1.78)
Metastatic women alive beyond 18 months								
HIV-	31/62	1.00	31/62	1.00	31/62	1.00	21/44	1.00
HIV+	6/13	0.73 (0.30-1.78)	6/13	1.14 (0.42-3.11)	6/13	1.08 (0.35-3.40)	5/11	1.22 (0.32-4.63)

HR: hazard ratio; CI: confidence interval

^α Model A: Cox regression model for HIV effect on all-cause model adjusted for age, stage and tumour grade at breast cancer diagnosis

^β Model B: Model A + others factors, namely socio economic position and formal education attained

^γ Model C: Model B + tumour receptor subtype (HR+, HER2-; HR+, HER2+; HR-, HER2+; HR-,HER2-), available for Namibia and South Africa only

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

	All sites		Namibia		South Africa		Uganda		Zambia ^α
	Non-metastatic	Metastatic	Non-metastatic	Metastatic	Non-metastatic	Metastatic	Non-metastatic	Metastatic	Non-metastatic
ASSUMPTION	HR (95% CI) ^β	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
HIV NK dropped									
HIV+ vs. HIV-	1.63	1.12	1.46	1.14	2.22	0.88	1.07	0.84	3.11
	(1.29-2.09)	(0.71-1.76)	(0.88-2.44)	(0.39-3.39)	(1.50-3.29)	(0.45-1.72)	(0.62-1.84)	(0.35-2.02)	(1.38-7.03)
HIV NK assumed HIV-positive									
HIV+ vs. HIV-	1.55	1.11	1.53	1.13	2.34	0.95	0.96	0.84	1.74
	(1.26-1.91)	(0.75-1.63)	(0.97-2.42)	(0.47-2.71)	(1.62-3.38)	(0.49-1.83)	(0.63-1.46)	(0.41-1.75)	(0.97-3.11)
HIV NK assumed to be negative									
HIV+ vs. HIV-	1.60	1.10	1.39	1.15	2.06	0.85	1.12	0.80	2.72
	(1.26-2.03)	(0.70-1.72)	(0.84-2.31)	(0.40-3.38)	(1.40-3.02)	(0.44-1.66)	(0.66-1.91)	(0.33-1.91)	(1.30-5.67)

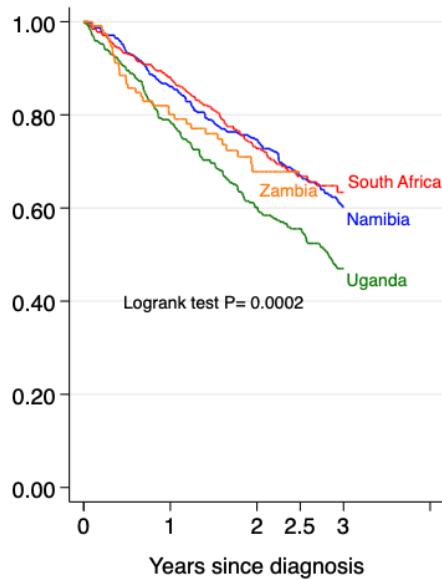
α: There were only 10 deaths/13 total women with metastatic disease overall in Zambia, hence not included

β: Hazard ratio and 95% confidence interval adjusted for age and tumour grade at diagnosis

γ: HIV NK: HIV status not known

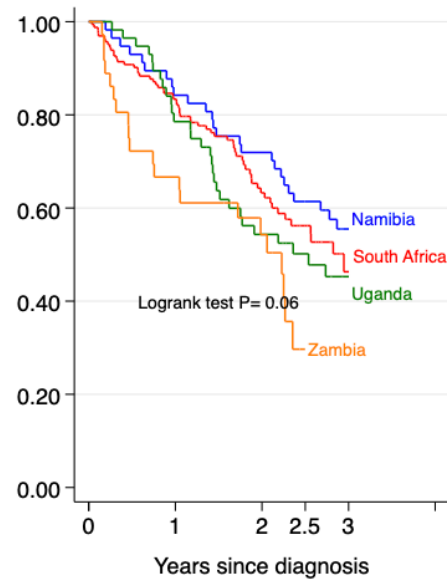
Supplementary Figure 1: Kaplan Meier curves for 3-year overall survival from breast cancer by country and separately for (a) HIV-negative women and (b) HIV-positive women in the ABC-DO HIVsubcohort

(a) HIV-negative women



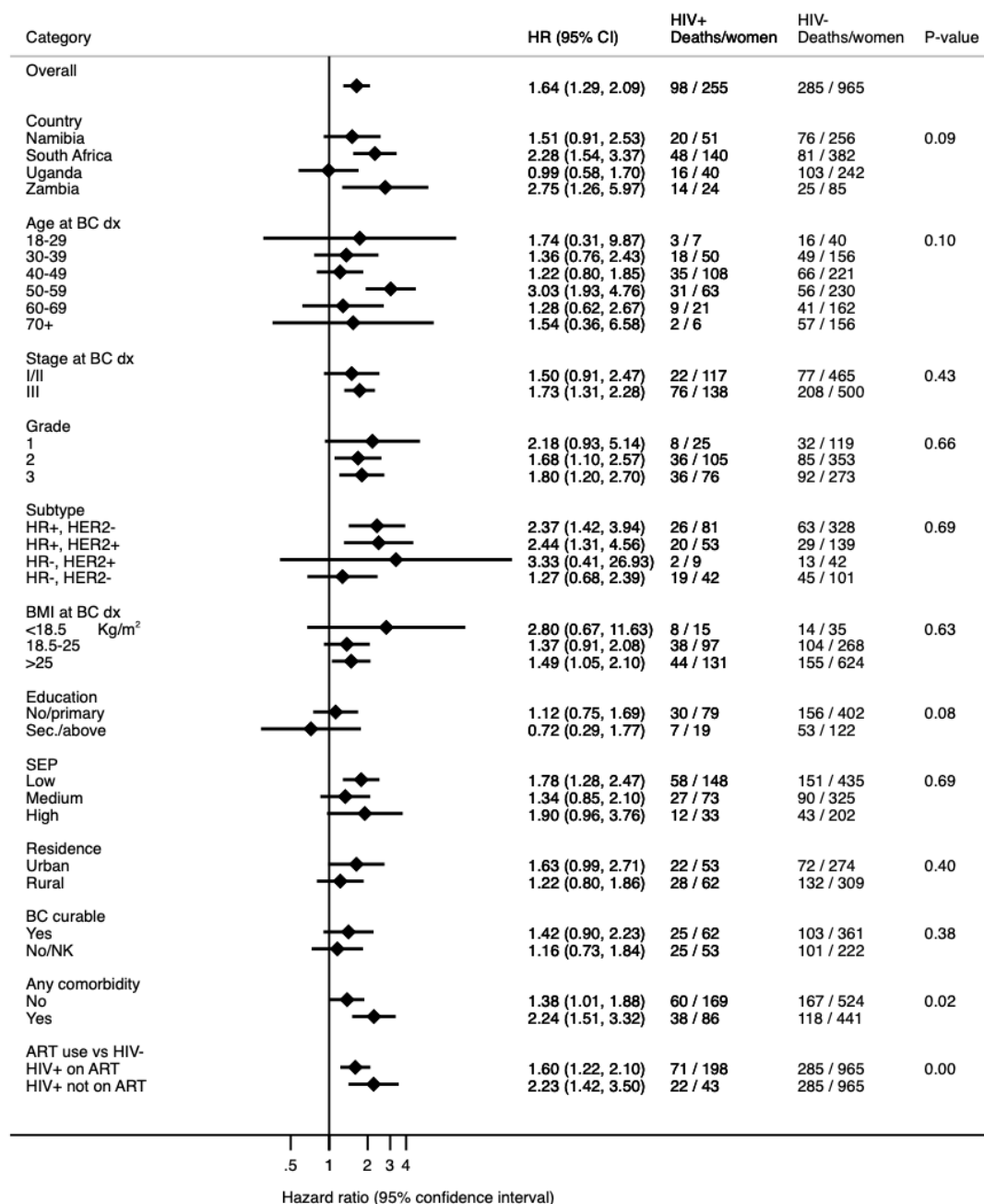
Number at risk	0	1	2	2.5	3
Namibia	309	266	228	189	139
South Africa	446	390	196	121	33
Uganda	315	245	176	144	95
Zambia	114	83	41	0	0

(b) HIV-positive women



Number at risk	0	1	2	2.5	3
Namibia	57	48	41	34	20
South Africa	163	135	60	34	12
Uganda	57	43	29	21	14
Zambia	36	24	15	0	0

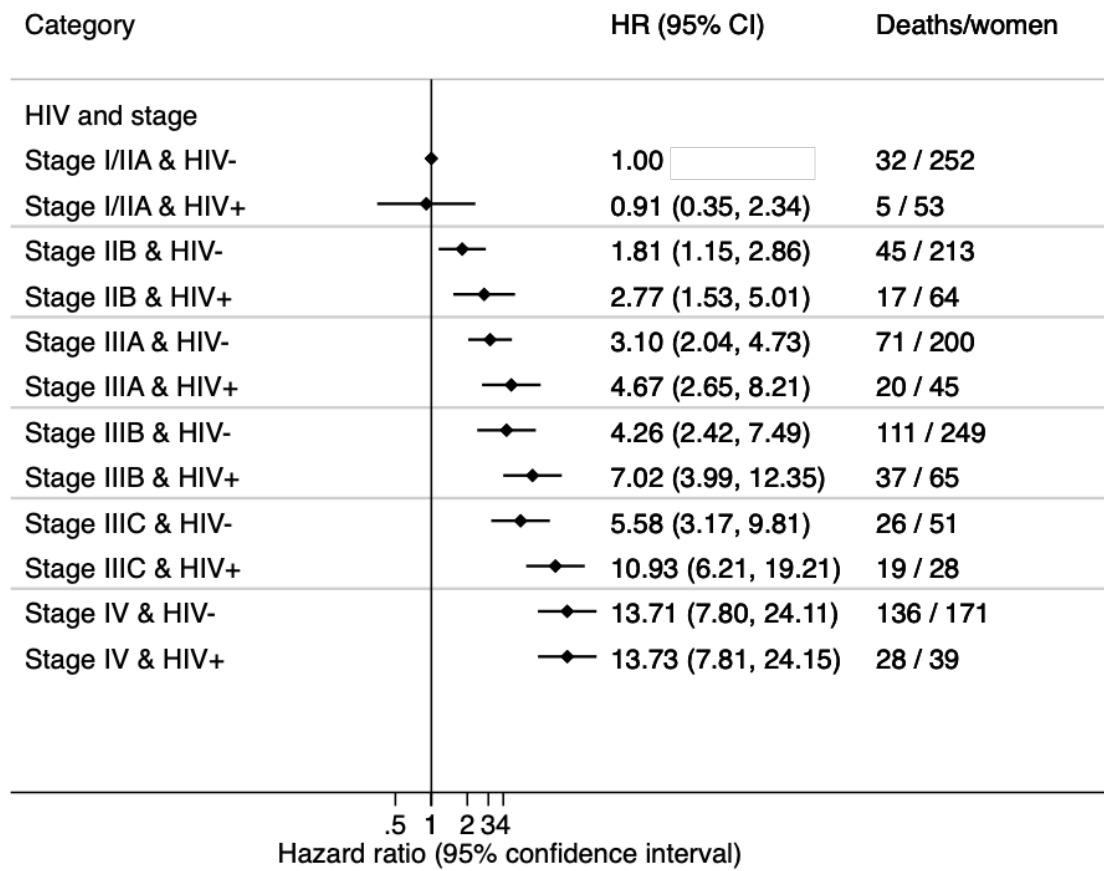
Supplementary Figure 2: Hazard ratios for all-cause mortality in HIV+ vs HIV- women among non-metastatic patients at breast cancer diagnosis, by patient and tumour characteristic in the ABC-DO HIV subcohort



Footnote:

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

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



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

REFERENCES

1. Coghill AE, Newcomb PA, Madeleine MM, Richardson BA, Mutyaba I, Okuku F, et al. Contribution of HIV infection to mortality among cancer patients in Uganda. *Aids*. 2013;27(18):2933-42.
2. Cubasch H, Dickens C, Joffe M, Duarte R, Murugan N, Tsai Chih M, et al. Breast cancer survival in Soweto, Johannesburg, South Africa: A receptor-defined cohort of women diagnosed from 2009 to 11. *Cancer Epidemiol*. 2018;52:120-7.
3. Sadigh K HR, Tapela N. HIV IS ASSOCIATED WITH DECREASED BREAST CANCER SURVIVAL: A PROSPECTIVE COHORT STUDY <http://www.croiconference.org/sessions/hiv-associated-decreased-breast-cancer-survival-prospective-cohort-study>: CROI Conference; 2019 [Accessed on 12/10/20]
4. Brandão M, Bruzzone M, Franzoi MA, de Angelis C, Eiger D, Caparica R, et al. Impact of HIV infection on baseline characteristics and survival of women with breast cancer: a systematic review and meta-analysis. *Aids*. 2020;Publish Ahead of Print.
5. McCormack V, McKenzie F, Foerster M, Zietsman A, Galukande M, Adisa C, et al. Breast cancer survival and survival gap apportionment in sub-Saharan Africa (ABC-DO): a prospective cohort study. *The Lancet Global Health*. 2020;8(9):e1203-e12.
6. Biggar RJ, Engels EA, Ly S, Kahn A, Schymura MJ, Sackoff J, et al. Survival after cancer diagnosis in persons with AIDS. *J Acquir Immune Defic Syndr*. 2005;39(3):293-9.
7. 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(21):2376-83.
8. 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(16):2868-76.
9. 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(9).
10. Chhatre S, Schapira M, Metzger DS, Jayadevappa R. Association between HIV infection and outcomes of care among medicare enrollees with breast cancer. *EClinicalMedicine*. 2019;17:100205.