DR. ANNA ELIZABETH COGHILL (Orcid ID : 0000-0001-7142-7499)

DR. AHMEDIN JEMAL (Orcid ID : 0000-0002-0000-4111)

DR. MEREDITH S SHIELS (Orcid ID : 0000-0001-8390-6091)

Article type : Original Article

Advanced Stage at Diagnosis and Elevated Mortality among HIV-infected US Cancer Patients in the National Cancer Database

Anna E. Coghill[1,2], Xuesong Han[3], Gita Suneja[4], Chun Chieh Lin[3,5], Ahmedin Jemal[3], Meredith S. Shiels[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda MD

[2]Cancer Epidemiology Program, H. Lee Moffitt Cancer Center & Research Institute, Tampa FL

[3]Surveillance and Health Services Research, American Cancer Society, Atlanta GA

[4]Radiation Oncology, Duke University, Durham NC

[5]Health Services Research Program, University of Michigan, Ann Arbor MI

Running Title: HIV-related tumor aggressiveness in NCDB

Corresponding Author:

Anna E. Coghill, PhD MPH

H. Lee Moffitt Cancer Center & Research Institute
13131 USF Magnolia Drive, Tampa, FL 33612
(813) 745-7147
anna.coghill@moffitt.org

Funding. This research was supported by the Intramural Research Programs of the National Cancer Institute (National Institutes of Health) and the American Cancer Society. Dr. Suneja is supported by grants K08CA228631 and P30AI064518 from the US National Institutes of Health.

Disclosures. Xuesong Han and Ahmedin Jemal are employed by the American Cancer Society, which receives grants from private and corporate foundations, including foundations associated with companies in the health sector for research outside the submitted work. The authors are not funded by or key personnel for any of these grants and their salary is solely funded through American Cancer Society funds. The other authors declared no conflicts of interest.

Previous presentation. This work was presented as a poster at the 16th International Conference on Malignancies in HIV/AIDS in Bethesda, MD in October 2017.

Keywords: HIV and cancer; cancer patient mortality; cancer stage; National Cancer Database; health insurance and mortality

Author contributions: Study conception and design (AEC, MS); Data analysis (XH, CCL); Data interpretation and manuscript preparation (AEC, XH, GS, CCL, AJ, MS)

Precis: People living with HIV are more likely to be diagnosed with advanced-stage cancers and to experience elevated mortality following their cancer diagnosis, even after accounting for healthcare-related factors.

ABSTRACT.

Background. People living with HIV (PLWH) are at increased risk for developing several cancers, but less is known about how HIV impacts the rate of progression to advanced cancer or death.

Methods. We compared stage at presentation and mortality after diagnosis between 14,453 PLWH and 6,368,126 HIV-uninfected patients diagnosed with cancers of the oral cavity, stomach, colorectum, anus, liver, pancreas, lung, female breast, cervix, prostate, bladder, kidney, thyroid, and melanoma using data from the National Cancer Database (2004-2014). Polytomous logistic regression and Cox proportional hazards regression were used to evaluate the association between HIV, cancer stage, and stage-adjusted mortality following diagnosis, respectively. Regression models accounted for the type health facility where cancer treatment was administered and type of individual health insurance.

Results. HIV-infected cancer patients were more likely to be uninsured (HIV-infected: 5·0% vs. HIV-uninfected: 3·3%; P<0·0001) and were less likely to have private health insurance (25·4% vs. 44·7%; P<0·0001). Compared to non-PLWH, the odds of being diagnosed at advanced stage were significantly elevated in PLWH for melanoma and cancers of the oral cavity, liver, female breast, prostate, and thyroid (OR for stage IV vs. stage I range:1·24-2·06). PLWH diagnosed with Stage I-III disease experienced elevated mortality following diagnosis across 13 of the 14 cancer sites evaluated, with hazard ratios ranging from 1·20 (95%CI 1·14-1·26) for lung cancer to 1·85 (1·68-2·04), 1·85 (1·51-2·27), and 2·93 (2·08-4·13) for female breast, cervix, and thyroid cancers, respectively.

Conclusion. PLWH were more likely to be diagnosed with advanced-stage cancers and to experience elevated mortality following cancer diagnosis, even after accounting for healthcare-related factors.

INTRODUCTION. People living with human immunodeficiency virus (PLWH) have an elevated risk of certain cancer types, particularly those caused by viral co-infections.[1-9] Rates of many infection-associated cancers among PLWH have declined following the widespread

availability of highly active antiretroviral therapy (HAART) to restore patient immunity, although risk remains elevated compared to HIV-uninfected persons.[10-13] Unlike infection-associated cancers, some non-infection-related cancers such as prostate, female breast, and colon do not occur at elevated rates in PLWH.[14] Nevertheless, these cancers are becoming increasingly prevalent among PLWH because of widespread dissemination of HAART that permits HIV patients to live to older ages when cancers are more common,[15, 16] raising the important question of whether HIV-related immunosuppression is associated with tumors that progress to higher stages before being diagnosed or result in poorer outcomes following diagnosis.

Both advanced stage at presentation and elevated mortality following diagnosis can reflect tumor aggressiveness, and recent data suggest that immunosuppressed patients fare worse on both metrics. A prior registry-based study showed that PLWH were more likely to be diagnosed with distant-stage cancers of the lung, female breast, prostate, bladder, and melanoma.[17] Stage-adjusted mortality following diagnosis was also elevated in a similar population of HIV-infected cancer patients across a range of sites, including cancers of the colorectum, pancreas, larynx, lung, female breast, prostate, and melanoma.[18] It is plausible that advanced-stage disease and elevated mortality following a cancer diagnosis among PLWH are related to the biological effects of HIV-associated immunosuppression.

However, the more advanced-stage cancers and elevated mortality reported among PLWH could also be related to receipt of sub-optimal healthcare, a possibility supported by mounting data that PLWH are less likely to receive cancer treatment.[19, 20] Available data have not been able to disentangle these possibilities. To begin addressing this issue of sub-optimal healthcare, we evaluated the association between HIV, cancer stage at presentation, and mortality after a cancer diagnosis after accounting for the type of treating health facility and reported individual health insurance using data from more than six million US cancer patients from the National Cancer Database.

METHODS. The National Cancer Database (NCDB) is a nationwide, hospital-based registry database jointly sponsored by the American Cancer Society and the American College of Surgeons. Using the NCDB, we ascertained the following primary, malignant cancers occurring in adults (≥18 years of age) between 2004-2014: oral cavity/pharynx/larynx (International Classification of Diseases [ICD] for Oncology version 3 topography codes C000-C009, C019-

C069, C079-C099, C100-C109, C110-C119, C129-C140, C142, C148, C320-C329), stomach (C160-C169), colorectum (C180-C189, C199, C209), anus (C210, C218), liver (C220), pancreas (C250-C259), lung (C340-C349), female breast (C500-C509), cervix (C530-C539), prostate (C619), bladder (C670-C679), kidney (C649, C659), thyroid (C739), and melanoma (C440-C449 with histology codes 8720-8790). Cancers with the following histology codes were excluded: 9050-9055, 9140, and 9590-9989. Patients with unknown stage, unknown date of diagnosis, or unknown last date of contact were also excluded.

The HIV status of each cancer patient at the time of cancer diagnosis was defined using ICD-9 codes, with HIV positivity defined as the presence of codes 04200-04499, 07953, or V08. Cancer stage at presentation was defined as stages I, II, III, or IV using the Collaborative Stage 6th edition (https://cancerstaging.org/cstage/Pages/default.aspx). Factors related to healthcare were ascertained from the NCDB database, including data on the type of health facility where cancer care was administered (community center, comprehensive community center, teaching/research institution, National Cancer Institute [NCI] network cancer center, integrated network, other/unknown, as defined by the Commission on Cancer [21]) and the type of reported health insurance (private, Medicaid, Medicare, no insurance, other government insurance). We hypothesized that the type of treating health facility reflects an important aspect of the quality of care received, whereas individual health insurance can influence a patient's access to care.

Statistical Analysis. We utilized polytomous logistic regression to estimate the association between HIV status and cancer stage at presentation (stage I as referent group), adjusting for patient sex (male, female), age (18-44, 45-54, 55-64, 65+ years), race (non-Hispanic white, black, Hispanic, other, missing), calendar year of cancer diagnosis (2004-2006, 2007-2010, 2011-2014), and median household income by zip code (<$38000, $38000-47999, $48000-62999, $63000+, missing). Analyses were conducted separately for each cancer site. P-trends were calculated by fitting logistic regression models with stage categorized as an ordinal variable, adjusting for the covariates listed above. To further assess whether any HIV and cancer stage associations were attributable to factors related to sub-optimal care, we adjusted for the type of health facility at which cancer treatment was received and the type of individual health insurance.

We next evaluated whether HIV was associated with overall mortality using Cox proportional hazards regression. Follow-up time for each cancer patient was calculated from the date of cancer diagnosis to the date of death from any cause, with follow-up ending in 2014. Cases diagnosed between 2013 and 2014 were excluded to ensure adequate follow-up time to ascertain mortality. These mortality analyses were limited to Stage I-III disease due to the heterogeneity of disease burden, treatment approaches, and outcomes that occur in patients with metastatic (Stage IV) disease. Analyses were adjusted for age, sex, race, calendar year of cancer diagnosis, median household income, cancer stage, and cancer treatment (categorized as yes/no for receipt of surgery, radiation or chemotherapy). Additional models were adjusted for type of treating health facility and type of individual health insurance. The proportional hazard assumption was tested by examining parallelism in ln(-ln(survival)) versus ln(time) plots. No violations of this assumption were observed for HIV across any cancer site. However, violations were observed for cancer stage and treatment, requiring time-dependent adjustment for these two variables in regression models.

In a supplemental analysis, we ran logistic and Cox models for cancer stage and mortality outcomes, respectively, within patient groups <65 years of age stratified by receipt of specific types of health insurance: (1) private insurance, (2) Medicare, or (3) Medicaid.

RESULTS. We compared cancer stage at presentation and mortality following cancer diagnosis in over six million US cancer patients from the NCDB, including 14,453 PLWH diagnosed with cancer between 2004 and 2014 (**Table 1**). HIV-infected cancer patients were younger, more likely to be male and non-white, and had lower median household income than HIV-uninfected cancer patients (P<0·0001). The most common cancer diagnoses in PLWH were lung cancer (29·1% of all cases), colorectal cancer (14·1%), and prostate cancer (10·5%), compared to cancers of the breast (22·8%), prostate (17·8%), and lung (17·7%) among HIV-uninfected patients, reflecting differences in the patient sex distribution by HIV status. We observed significant differences in the proportion of uninsured cancer patients by HIV status (HIV-infected: 5·0% vs. HIV-uninfected: 3·3%; P<0·0001), with PLWH being approximately half as likely to report private health insurance (HIV-infected: 25·4% vs. HIV-uninfected: 44·7%) and approximately 3 times more likely to be on Medicaid (HIV-infected: 17·9% vs. HIV-uninfected: 5·9%). The likelihood of receiving cancer treatment and the type of health facility at which treatment was administered also differed by HIV status (P<0·0001).

PLWH were more likely (*P*-trend <0·05) to be diagnosed with advanced-stage cancers of the oral cavity, liver, female breast, prostate, thyroid, and melanoma (**Table 2**). After adjustment for both the type of treating healthcare facility and individual health insurance, statistically significant trends toward later-stage disease remained, with the association between HIV and Stage IV disease (vs. Stage I) ranging from 1·24 (95%CI 1·02-1·52) for liver cancer to 2·06 (1·70-2·50) for female breast cancer. Of note, HIV was associated with marginally earlier stage at diagnosis for colorectal cancer (Stage IV vs. Stage I: OR=0·89 95%CI 0·78-1·02; *P*-trend=0·03) and substantially earlier stage anal cancer (OR=0·54; 0·41-0·73; *P*-trend<0·01). After restricting analyses to patients <65 years of age and stratifying by receipt of either private insurance, Medicare, or Medicaid, results were largely consistent (**Supplemental Table 1**). Interestingly, the association between HIV and advanced-stage breast cancer was more pronounced among women with private insurance (OR=2·22) or Medicare (OR=2·27), groups assumed to have good access to care, compared to 0·77 in women with Medicaid. The association between HIV and advanced-stage stomach and kidney cancer was not significant overall but was strongly positive among patients with Medicare (stomach: OR=3·46 95%CI 1·67-7·48; kidney: 1·85; 1·09-3·15).

Among patients with Stage I-III disease, HIV was significantly associated with elevated mortality after a cancer diagnosis for 13 of the 14 sites evaluated, even after adjustment for stage at diagnosis, first-course cancer treatment modality, type of treating cancer facility, and type of individual health insurance (**Table 3; Supplemental Table 2**). The strength of the association between HIV and overall mortality ranged from HRs of 1·20 (95%CI 1·14-1·26) for lung cancer to 1·85 (1·68-2·04), 1·85 (1·51-2·27), and 2·93 (2·08-4·13) for female breast, cervix, and thyroid cancers, respectively. The five cancers with the most pronounced HIV-associated elevations in mortality following diagnosis are illustrated in **Figure 1** and include both virus-associated and non-virus-associated tumors. We also confirmed that PLWH experienced significantly elevated mortality even after including patients with metastatic (Stage IV) disease (**Supplemental Table 3**).

DISCUSSION. Our data on more than six million US cancer patients is consistent with PLWH experiencing a more aggressive disease course for cancer – we report significant associations between HIV and both advanced stage at presentation and elevated mortality following

diagnosis. Specifically, PLWH were significantly more likely to be diagnosed with advanced-stage cancers of the oral cavity, liver, female breast, prostate, thyroid, and melanoma. Furthermore, HIV was associated with elevated mortality after a cancer diagnosis for 13 of the 14 cancer sites evaluated, including an almost doubling and tripling of mortality for female breast and thyroid cancers, respectively. The persistence of these associations after adjustment for factors related to receipt of healthcare provides support for a biological link between HIV-related immunosuppression and cancer progression.

Only one prior study broadly examined cancer stage in PLWH; in that study, HIV was associated with more advanced stage in patients with cancers of the lung, breast, prostate, bladder, and melanoma.[17] However, that study did not have information on type of care received by HIV status. To mitigate this fact, the authors compared results with those observed among solid organ transplant recipients, an immunosuppressed patient group that, unlike PLWH, has increased utilization of health care. Consistent results for more advanced-stage diagnoses of bladder cancer and melanoma suggested a possible biological role for immunosuppression in the progression of these cancers. Our current study was unique in that availability of information on health insurance in NCDB enabled us to more directly address potential non-biological explanations for later-stage cancer diagnosis in PLWH. We confirmed prior associations between HIV and later-stage breast cancer, prostate cancer, and melanoma.[17] In addition, we report associations between HIV and advanced-stage oral cavity, liver and thyroid cancers. Since these associations were independent of the type of health insurance a patient reported, it appears that access to healthcare is not the sole explanation for the stage shifts.

Our results do highlight one notable exception – PLWH were substantially more likely to be diagnosed with less advanced anal cancers than their HIV-uninfected counterparts. This potentially represents an example of increased healthcare being directed to the HIV population, a distinct possibility given the ongoing targeting of anal cancer screening procedures to HIV-infected men who have sex with men.[22] Importantly, even though these immunosuppressed patients were more likely to be diagnosed with less-advanced disease, their stage-adjusted mortality was higher than HIV-uninfected patients. Mortality following an anal cancer diagnosis was ~40% higher in PLWH compared to HIV-uninfected patients diagnosed with the same disease stage in our study.

The association of HIV with elevated mortality following a cancer diagnosis was present for Stage I-III tumors regardless of their initiating etiology. Elevations in cancer patient mortality ranged from 20% (lung cancer) to ~3-fold (thyroid cancer) in PLWH, with the largest HIV-related differences observed for cancers with a generally good prognosis (e.g., breast and thyroid cancer).[23] These data are consistent with prior work showing higher rates of cancer patient mortality in the setting of HIV.[18, 24-26] However, this study not only accounted for clinically-important prognostic factors such as cancer stage and treatment, but also demonstrated higher mortality in HIV-infected cancer patients after accounting for the type of treating health facility (quality of cancer care) and individual health insurance (access to care). Further, the NCDB includes only cancer patients who at least initiated cancer care, as opposed to our prior study that included diagnoses of cancer among all PLWH, regardless of healthcare utilization.[18]

Ultimately, cancer patients with the same stage at presentation, same initial treatment modality, reporting similar health insurance, and receiving cancer care at the same type of healthcare facility still died more often if they were HIV-infected at the time of cancer diagnosis. A biological explanation for this persistent effect of immunosuppression on cancer patient outcomes is plausible when considered alongside data suggesting that immunosuppressed solid organ transplant recipients also experience elevated mortality after a cancer diagnosis,[27] recent advances in cancer survival associated with immune-boosting therapies,[28-30] and data suggesting that additional cancer-specific outcomes (i.e., relapse after successful first-course treatment) are poorer in the presence of HIV.[31] However, it must be acknowledged that this evaluation focused on overall mortality as the clinically-relevant outcome rather than death due specifically to cancer. It is possible that PLWH in this study died more often due in part to a higher risk of additional causes of death, including AIDS and other HIV-associated comorbidities.

Our study is notable not only for the size and national scope of the NCDB but also because prior studies have not been able to examine the possibility that variation in receipt of healthcare could offer a non-biological explanation for more advanced-stage cancer and elevated mortality following cancer diagnosis among PLWH. Instead of proving a non-biological explanation for the link between HIV and the chosen metrics of tumor aggressiveness – advanced stage and elevated mortality – our data suggest that biology could underlie this association.

Certain limitations of this study should be noted. First, we cannot rule out the possibility of HIV-related differences in access to healthcare that we were not able to account for in our models. For example, our classification of insurance into large groupings (e.g., private insurance) may have failed to adequately adjust for variation according to insurance provider or coverage levels. Simple adjustment for receipt of health insurance also likely did not capture variation in the utilization of health services (i.e., having and using insurance are not equivalent). Additional misclassification may have also existed for our exposure - hospital discharge diagnoses likely under-ascertain HIV status. As noted above, our evaluation of overall mortality following a cancer diagnosis was not able to capture potentially important HIV-related differences in cancer-specific mortality. Finally, we were not able to address the association between clinical measures of immunosuppression (e.g., CD4 count) or HIV treatment (e.g., anti-retroviral therapy) and outcomes as NCDB does not collect this information. Future studies that include clinical HIV data should evaluate these more refined metrics of patient immune status.

In summary, in our study of over six million US cancer patients, those infected with HIV were more likely to be diagnosed with advanced-stage cancers of the oral cavity, liver, female breast, prostate, thyroid, and melanoma. PLWH diagnosed with Stage I-III cancer also experienced elevated mortality following diagnosis across a range of tumor etiologies. These associations persisted in PLWH even after accounting for HIV-related differences in the type of treating cancer facility and patient-reported individual health insurance. Although the possibility remains that our findings could be partly explained by differences in healthcare utilization, differences in applied cancer treatment, or mortality from non-cancer comorbidities, our results support a possible biological association between HIV and tumor behavior.

ACKNOWLEDGEMENTS. The data used in the study are derived from a limited data set of the National Cancer Data Base (NCDB). The authors acknowledge the efforts of the American College of Surgeons, the Commission on Cancer, and the American Cancer Society in the creation of the National Cancer Data Base. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the authors.

FIGURE 1 LEGEND. Hazard ratios (HR) illustrating the association between HIV status and mortality following a cancer diagnosis for the five cancer sites with the strongest effect estimates, according to the type of individual health insurance reported

Table 1. Characteristics of patients in the National Cancer Database (2004-2014), according to HIV status

Demographic Factors		Total (N=6382579) N (%)	HIV-infected (N=14453) N (%)	HIV-uninfected (N=6368126) N (%)	Chi-square p value
Sex					
	Male	3146045 (49.3)	9296 (64.3)	3136749 (49.3)	p < 0.0001
	Female	3236534 (50.7)	5157 (35.7)	3231377 (50.7)	
Age at diagnosis (years)					
	18-44	543310 (8.5)	1452 (10)	541858 (8.5)	p < 0.0001
	45-54	1075558 (16.9)	3513 (24.3)	1072045 (16.8)	
	55-64	1733796 (27.2)	3597 (24.9)	1730199 (27.2)	
	65+	3029915 (47.5)	5891 (40.8)	3024024 (47.5)	
Race/Ethnicity					
	White, non-Hispanic	4726015 (74.0)	7966 (55.1)	4718049 (74.1)	p < 0.0001
	Black	328450 (5.1)	1054 (7.3)	327396 (5.1)	
	Hispanic	689689 (10.8)	4533 (31.4)	685156 (10.8)	
	Other	206283 (3.3)	177 (1.2)	206106 (3.3)	
	Missing	432142 (6.8)	723 (5)	431419 (6.8)	
Year of cancer diagnosis					
	2004-2006	1628351 (25.5)	5141 (35.6)	1623210 (25.5)	p < 0.0001
	2007-2010	2366096 (37.1)	5912 (40.9)	2360184 (37.1)	
	2011-2014	2388132 (37.4)	3400 (23.5)	2384732 (37.4)	
Median income level [a]					
	<$38000	1120358 (17.6)	4150 (28.7)	1116208 (17.5)	p < 0.0001
	$38000-$47999	1466892 (23)	3280 (22.7)	1463612 (23)	
	$48000-$62999	1676914 (26.3)	3254 (22.5)	1673660 (26.3)	
	$63000+	2013696 (31.5)	3444 (23.8)	2010252 (31.6)	
	Missing	104719 (1.6)	325 (2.2)	104394 (1.6)	
Cancer site					
	Oral Cavity/Pharynx/Larynx	289643 (4.5)	939 (6.5)	288704 (4.5)	p < 0.0001
	Stomach	106060 (1.7)	290 (2)	105770 (1.7)	
	Colorectum	784001 (12.3)	2034 (14.1)	781967 (12.3)	
	Anus	30793 (0.5)	1052 (7.3)	29741 (0.5)	
	Liver	107544 (1.7)	823 (5.7)	106721 (1.7)	
	Pancreas	211219 (3.3)	498 (3.4)	210721 (3.3)	
	Lung	1130306 (17.7)	4201 (29.1)	1126105 (17.7)	
	Melanoma	263127 (4.1)	214 (1.5)	262913 (4.1)	

Female Breast	1449954 (22.7)	1197 (8.3)	1448757 (22.8)	
Cervix	95222 (1.5)	330 (2.3)	94892 (1.5)	
Prostate	1136297 (17.8)	1513 (10.5)	1134784 (17.8)	
Bladder	176320 (2.8)	394 (2.7)	175926 (2.8)	
Kidney	314810 (4.9)	708 (4.9)	314102 (4.9)	
Thyroid	287283 (4.5)	260 (1.8)	287023 (4.5)	
Individual insurance status				
Private	2852824 (44.7)	3667 (25.4)	2849157 (44.7)	p < 0.0001
Medicaid	380678 (6.0)	2587 (17.9)	378091 (5.9)	
Medicare	2770671 (43.4)	7234 (50.0)	2763437 (43.5)	
Uninsured	211643 (3.3)	717 (5.0)	210926 (3.3)	
Government	34223 (0.5)	72 (0.5)	34151 (0.5)	
Missing	132540 (2.1)	176 (1.2)	132364 (2.1)	
Type of treating health facility				
Community center	628450 (9.8)	1410 (9.8)	627040 (9.8)	p < 0.0001
Comprehensive community center	2712165 (42.5)	5435 (37.6)	2706730 (42.5)	
Teaching/research institution	1466395 (23)	3833 (26.5)	1462562 (23)	
NCI network cancer center	731239 (11.5)	1774 (12.3)	729465 (11.5)	
Integrated Network	649528 (10.2)	1463 (10.1)	648065 (10.2)	
Others/Unknown	194802 (3.1)	538 (3.7)	194264 (3.1)	
Receipt of surgery, radiation or chemotherapy				
Yes	5758785 (90.2)	11598 (80.2)	5747187 (90.3)	p < 0.0001
No	610101 (9.6)	2802 (19.4)	607299 (9.5)	
Unknown	13693 (0.2)	53 (0.4)	13640 (0.2)	

[a] Sums to less than 100% due to missing data

Table 2. Odds Ratios (ORs) and 95% confidence intervals (CIs) describing the association between patient HIV status and stage of disease at diagnosis

Cancer Site		Total Cases (N%)	HIV-infected cases (N,%)	HIV-uninfected cases (N,%)	Model 1, not adjusted for healthcare factors [a]	Model 2, adjusted for healthcare factors [b]
Oral Cavity/Pharynx/Larynx						
	Stage I	65128 (22.5)	127 (13.5)	65001 (22.5)	1	1
	Stage II	38100 (13.2)	108 (11.5)	37992 (13.2)	1.32(1.02,1.71)	1.24(0.96,1.6)
	Stage III	50123 (17.3)	176 (18.7)	49947 (17.3)	1.52(1.21,1.91)	1.38(1.1,1.74)
	Stage IV	136292 (47.1)	528 (56.2)	135764 (47.0)	1.54(1.27,1.88)	1.35(1.1,1.64)
	P-trend				**0.0001** [c]	**0.0134**
Stomach						
	Stage I	28157 (26.5)	76 (26.2)	28081 (26.5)	1	1
	Stage II	15341 (14.5)	43 (14.8)	15298 (14.5)	1.01(0.69,1.47)	1.03(0.71,1.5)
	Stage III	15783 (14.9)	39 (13.4)	15744 (14.9)	0.83(0.56,1.23)	0.85(0.58,1.26)
	Stage IV	46779 (44.1)	132 (45.5)	46647 (44.1)	0.95(0.71,1.26)	0.94(0.71,1.26)
	P-trend				0.7826	0.7070
Colorectum						
	Stage I	181014 (23.1)	465 (22.9)	180549 (23.1)	1	1
	Stage II	208371 (26.6)	616 (30.3)	207755 (26.6)	1.16(1.03,1.31)	1.13(1,1.27)
	Stage III	227004 (29.0)	557 (27.4)	226447 (29.0)	1(0.88,1.13)	0.98(0.87,1.11)
	Stage IV	167612 (21.4)	396 (19.5)	167216 (21.4)	0.94(0.82,1.08)	0.89(0.78,1.02)
	P-trend				0.1559	**0.0313**
Anus						
	Stage I	6130 (19.9)	229 (21.8)	5901 (19.8)	1	1
	Stage II	11996 (39.0)	385 (36.6)	11611 (39.0)	0.86(0.72,1.02)	0.83(0.7,0.99)
	Stage III	10064 (32.7)	369 (35.1)	9695 (32.6)	0.9(0.76,1.08)	0.86(0.72,1.03)
	Stage IV	2603 (8.5)	69 (6.6)	2534 (8.5)	0.57(0.43,0.76)	0.54(0.41,0.73)
	P-trend				**0.0100**	**0.0027**
Liver						
	Stage I	38333 (35.6)	242 (29.4)	38091 (35.7)	1	1
	Stage II	21727 (20.2)	165 (20.0)	21562 (20.2)	1.1(0.9,1.35)	1.09(0.89,1.33)
	Stage III	27884 (25.9)	246 (29.9)	27638 (25.9)	1.27(1.06,1.52)	1.31(1.09,1.57)
	Stage IV	19600 (18.2)	170 (20.7)	19430 (18.2)	1.19(0.97,1.45)	1.24(1.02,1.52)

	P-trend				**0.0309**	**0.0084**
Pancreas						
	Stage I	17995 (8.5)	46 (9.2)	17949 (8.5)	1	1
	Stage II	62661 (29.7)	142 (28.5)	62519 (29.7)	0.84(0.6,1.17)	0.84(0.6,1.17)
	Stage III	22989 (10.9)	45 (9.0)	22944 (10.9)	0.65(0.43,0.99)	0.65(0.43,0.98)
	Stage IV	107574 (50.9)	265 (53.2)	107309 (50.9)	0.83(0.6,1.13)	0.82(0.6,1.13)
	P-trend				0.5813	0.5703
Lung						
	Stage I	238623 (21.1)	790 (18.8)	237833 (21.1)	1	1
	Stage II	63768 (5.6)	224 (5.3)	63544 (5.6)	0.91(0.79,1.06)	0.92(0.79,1.07)
	Stage III	293173 (25.9)	1090 (25.9)	292083 (25.9)	0.94(0.85,1.03)	0.93(0.84,1.01)
	Stage IV	534742 (47.3)	2097 (49.9)	532645 (47.3)	0.97(0.89,1.05)	0.97(0.89,1.05)
	P-trend				0.8945	0.9718
Melanoma						
	Stage I	172448 (65.5)	110 (51.4)	172338 (65.5)	1	1
	Stage II	42586 (16.2)	35 (16.4)	42551 (16.2)	1.12(0.77,1.65)	1.05(0.71,1.54)
	Stage III	32356 (12.3)	38 (17.8)	32318 (12.3)	1.52(1.05,2.21)	1.41(0.97,2.06)
	Stage IV	15737 (6.0)	31 (14.5)	15706 (6.0)	2.37(1.58,3.56)	1.96(1.3,2.97)
	P-trend				**<0.0001**	**0.0022**
Female breast						
	Stage I	692293 (47.7)	453 (37.8)	691840 (47.8)	1	1
	Stage II	502964 (34.7)	419 (35)	502545 (34.7)	1.2(1.05,1.37)	1.16(1.02,1.33)
	Stage III	179480 (12.4)	185 (15.5)	179295 (12.4)	1.36(1.14,1.62)	1.26(1.06,1.5)
	Stage IV	75217 (5.2)	140 (11.7)	75077 (5.2)	2.36(1.95,2.85)	2.06(1.70,2.50)
	P-trend				**<0.0001**	**<0.0001**
Cervix						
	Stage I	45105 (47.4)	146 (44.2)	44959 (47.4)	1	1
	Stage II	14506 (15.2)	53 (16.1)	14453 (15.2)	1.2(0.87,1.65)	1.05(0.76,1.45)
	Stage III	22528 (23.7)	78 (23.6)	22450 (23.7)	1.05(0.79,1.38)	0.92(0.69,1.22)
	Stage IV	13083 (13.7)	53 (16.1)	13030 (13.7)	1.42(1.03,1.96)	1.22(0.88,1.69)
	P-trend				0.0866	0.5754
Prostate						

	Stage I/II [d]	939405 (82.7)	1190 (78.7)	938215 (82.7)	1	1
	Stage III	115700 (10.2)	135 (8.9)	115565 (10.2)	0.97(0.82,1.17)	0.96(0.8,1.15)
	Stage IV	81192 (7.1)	188 (12.4)	81004 (7.1)	1.81(1.55,2.12)	1.57(1.34,1.83)
	P-trend				**<0.0001**	**<0.0001**
Bladder						
	Stage I	81514 (46.2)	170 (43.1)	81344 (46.2)	1	1
	Stage II	46726 (26.5)	118 (29.9)	46608 (26.5)	1.2(0.95,1.52)	1.19(0.94,1.5)
	Stage III	18135 (10.3)	36 (9.1)	18099 (10.3)	0.9(0.63,1.29)	0.89(0.62,1.28)
	Stage IV	29945 (17.0)	70 (17.8)	29875 (17.0)	1.04(0.78,1.38)	1(0.75,1.33)
	P-trend				0.7419	0.8901
Kidney						
	Stage I	185725 (59.0)	412 (58.2)	185313 (59.0)	1	1
	Stage II	28666 (9.1)	56 (7.9)	28610 (9.1)	0.81(0.61,1.08)	0.84(0.64,1.11)
	Stage III	46784 (14.9)	105 (14.8)	46679 (14.9)	1.05(0.85,1.31)	1.07(0.86,1.33)
	Stage IV	53635 (17.0)	135 (19.1)	53500 (17.0)	1.09(0.89,1.32)	1.06(0.87,1.3)
	P-trend				0.6677	0.6752
Thyroid						
	Stage I	207173 (72.1)	149 (57.3)	207024 (72.1)	1	1
	Stage II	23217 (8.1)	23 (8.8)	23194 (8.1)	0.94(0.59,1.48)	0.92(0.58,1.45)
	Stage III	35457 (12.3)	42 (16.2)	35415 (12.3)	1.23(0.85,1.78)	1.15(0.8,1.67)
	Stage IV	21436 (7.5)	46 (17.7)	21390 (7.5)	1.95(1.36,2.81)	1.67(1.16,2.41)
	P-trend				**0.0007**	**0.0072**

[a] Model 1 adjustment: age, sex, race, calendar year of cancer diagnosis, median household income (by zip code)

[b] Model 2 adjustment: age, sex, race, calendar year of cancer diagnosis, median household income (by zip code), patient-reported individual health insurance, type of treating cancer facility

[c] Bolded text denotes statistical significant for the P-trend test describing the likelihood of diagnosis with more advanced stages of disease by HIV status

[d] Individual stage groupings with less than 10 patients collapsed into categories to provide more stable effect estimates (e.g., stage I and stage II prostate cancer patients combined into stage I/II disease)

Table 3. Hazard Ratios (HRs) and 95% confidence intervals (CIs) describing the association between patient HIV status and mortality following cancer diagnosis

Cancer Site	Total Cases	Deaths (% of cases)	Model 1, not adjusted for healthcare factors [a]	Model 2, adjusted for healthcare factors [b]
Oral Cavity/Pharynx/Larynx				

	HIV-infected	353	194 (55.0%)	1.89(1.64,2.18)	1.66(1.44,1.92)
	HIV-uninfected	123760	44303 (35.8%)	1	1
Stomach					
	HIV-infected	141	106 (75.2%)	1.25(1.03,1.52)	1.20(0.98,1.45)
	HIV-uninfected	47263	28895 (61.1%)	1	1
Colorectum					
	HIV-infected	1524	903 (59.3%)	1.65(1.54,1.76)	1.58(1.48,1.69)
	HIV-uninfected	505650	181240 (35.8%)	1	1
Anus					
	HIV-infected	764	319 (41.8%)	1.56(1.38,1.76)	1.34(1.19,1.52)
	HIV-uninfected	21032	6601 (31.4%)	1	1
Liver					
	HIV-infected	515	422 (81.9%)	1.32(1.19,1.46)	1.29(1.16,1.42)
	HIV-uninfected	65652	46977 (71.6%)	1	1
Pancreas					
	HIV-infected	212	198 (93.4%)	1.37(1.19,1.59)	1.34(1.16,1.54)
	HIV-uninfected	81115	67982 (83.8%)	1	1
Lung					
	HIV-infected	1908	1547 (81.1%)	1.24(1.18,1.3)	1.20(1.14,1.26)
	HIV-uninfected	483000	340444 (70.5%)	1	1
Melanoma					
	HIV-infected	145	57 (39.3%)	1.79(1.38,2.32)	1.65(1.27,2.14)
	HIV-uninfected	194402	37221 (19.1%)	1	1
Female Breast					
	HIV-infected	957	399 (41.7%)	1.98(1.80,2.19)	1.85(1.68,2.04)
	HIV-uninfected	1099101	173881 (15.8%)	1	1
Cervix					
	HIV-infected	218	95 (43.6%)	2.06(1.68,2.52)	1.85(1.51,2.27)
	HIV-uninfected	67181	17506 (26.1%)	1	1
Prostate					
	HIV-infected	1170	236 (20.2%)	1.65(1.46,1.88)	1.56(1.37,1.77)
	HIV-uninfected	901852	112889 (12.5%)	1	1
Bladder					

	HIV-infected	302	217 (71.9%)	1.71(1.50,1.96)	1.66(1.45,1.9)
	HIV-uninfected	117311	57533 (49.0%)	1	1
Kidney					
	HIV-infected	514	204 (39.7%)	1.52(1.32,1.75)	1.41(1.22,1.62)
	HIV-uninfected	205898	45884 (22.3%)	1	1
Thyroid					
	HIV-infected	190	33 (17.4%)	3.10(2.20,4.37)	2.93(2.08,4.13)
	HIV-uninfected	206656	7841 (3.8%)	1	1

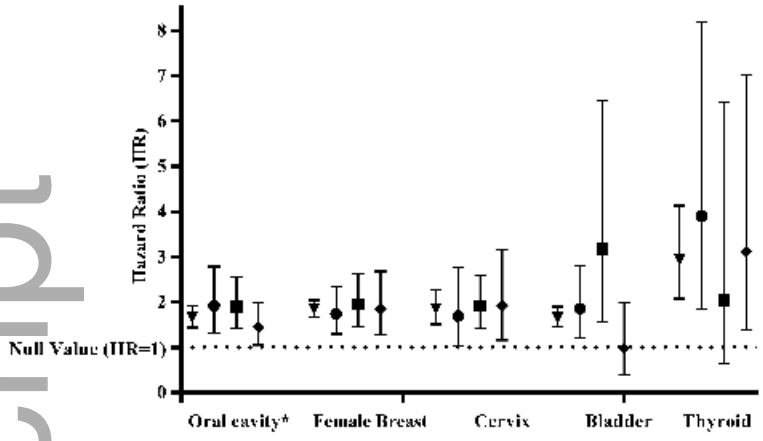
a Model 1 adjustment: age, sex, race, calendar year of cancer diagnosis, median household income (by zip code), cancer stage and treatment

b Model 2 adjustment: Model 1 + type of individual health insurance and treating cancer facility

1. Frisch M, Biggar RJ, Engels EA, Goedert JJ. Association of cancer with AIDS-related immunosuppression in adults. JAMA. 2001;285: 1736-1745.
2. Bedimo RJ, McGinnis KA, Dunlap M, Rodriguez-Barradas MC, Justice AC. Incidence of non-AIDS-defining malignancies in HIV-infected versus noninfected patients in the HAART era: impact of immunosuppression. J Acquir Immune Defic Syndr. 2009;52: 203-208.
3. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. J Natl Cancer Inst. 2009;101: 1120-1130.
4. Bruyand M, Thiebaut R, Lawson-Ayayi S, et al. Role of uncontrolled HIV RNA level and immunodeficiency in the occurrence of malignancy in HIV-infected patients during the combination antiretroviral therapy era: Agence Nationale de Recherche sur le Sida (ANRS) CO3 Aquitaine Cohort. Clin Infect Dis. 2009;49: 1109-1116.
5. Silverberg MJ, Chao C, Leyden WA, et al. HIV infection, immunodeficiency, viral replication, and the risk of cancer. Cancer Epidemiol Biomarkers Prev. 2011;20: 2551-2559.
6. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet. 2007;370: 59-67.
7. Hernandez-Ramirez RU, Shiels MS, Dubrow R, Engels EA. Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study. Lancet HIV. 2017.
8. Engels EA, Biggar RJ, Hall HI, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. Int J Cancer. 2008;123: 187-194.
9. Bertisch B, Franceschi S, Lise M, et al. Risk factors for anal cancer in persons infected with HIV: a nested case-control study in the Swiss HIV Cohort Study. Am J Epidemiol. 2013;178: 877-884.
10. Engels EA, Pfeiffer RM, Goedert JJ, et al. Trends in cancer risk among people with AIDS in the United States 1980-2002. Aids. 2006;20: 1645-1654.
11. Eltom MA, Jemal A, Mbulaiteye SM, Devesa SS, Biggar RJ. Trends in Kaposi's sarcoma and non-Hodgkin's lymphoma incidence in the United States from 1973 through 1998. J Natl Cancer Inst. 2002;94: 1204-1210.
12. Jacobson LP, Yamashita TE, Detels R, et al. Impact of potent antiretroviral therapy on the incidence of Kaposi's sarcoma and non-Hodgkin's lymphomas among HIV-1-infected individuals. Multicenter AIDS Cohort Study. J Acquir Immune Defic Syndr. 1999;21 Suppl 1: S34-41.
13. Robbins HA, Shiels MS, Pfeiffer RM, Engels EA. Epidemiologic contributions to recent cancer trends among HIV-infected people in the United States. Aids. 2014;28: 881-890.
14. Coghill AE, Engels EA, Schymura MJ, Mahale P, Shiels MS. Risk of Breast, Prostate, and Colorectal Cancer Diagnoses Among HIV-Infected Individuals in the United States. J Natl Cancer Inst. 2018.
15. Shiels MS, Pfeiffer RM, Gail MH, et al. Cancer Burden in the HIV-Infected Population in the United States. J Natl Cancer Inst. 2011;103: 753-762.
16. Shiels MS, Islam JY, Rosenberg PS, Hall HI, Jacobson E, Engels EA. Projected Cancer Incidence Rates and Burden of Incident Cancer Cases in HIV-Infected Adults in the United States Through 2030. Ann Intern Med. 2018;168: 866-873.
17. Shiels MS, Copeland G, Goodman MT, et al. Cancer stage at diagnosis in patients infected with the human immunodeficiency virus and transplant recipients. Cancer. 2015;121: 2063-2071.
18. Coghill A, Shiels MS, Suneja G, Engels EA. Elevated Cancer-specific Mortality among HIV-infected Persons in the US. Journal of Clinical Oncology. 2015;In Press.

19. Suneja G, Boyer M, Yehia BR, et al. Cancer Treatment in Patients With HIV Infection and Non-AIDS-Defining Cancers: A Survey of US Oncologists. J Oncol Pract. 2015;11: e380-387.
20. Suneja G, Shiels MS, Angulo R, et al. Cancer treatment disparities in HIV-infected individuals in the United States. J Clin Oncol. 2014;32: 2344-2350.
21. Commission on Cancer. Available from URL: https://www.facs.org/quality-programs/cancer/coc/apply/categories).
22. Palefsky JM. Screening to prevent anal cancer: Current thinking and future directions. Cancer Cytopathol. 2015;123: 509-510.
23. Zucchetto A, Virdone S, Taborelli M, et al. Non-AIDS-Defining Cancer Mortality: Emerging Patterns in the Late HAART Era. J Acquir Immune Defic Syndr. 2016;73: 190-196.
24. Chao C, Xu L, Abrams D, et al. Survival of non-Hodgkin lymphoma patients with and without HIV infection in the era of combined antiretroviral therapy. Aids. 2010;24: 1765-1770.
25. Marcus JL, Chao C, Leyden WA, et al. Survival Among HIV-Infected and HIV-Uninfected Individuals with Common Non-AIDS-Defining Cancers. Cancer Epidemiol Biomarkers Prev. 2015.
26. Sigel K, Crothers K, Dubrow R, et al. Prognosis in HIV-infected patients with non-small cell lung cancer. Br J Cancer. 2013;109: 1974-1980.
27. D'Arcy M. Survival after cancer diagnosis among solid organ transplant recipients. Cancer. 2018;In Press.
28. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363: 711-723.
29. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372: 320-330.
30. Postow MA, Callahan MK, Wolchok JD. Immune Checkpoint Blockade in Cancer Therapy. J Clin Oncol. 2015.
31. Ferreira MP, Coghill AE, Chaves CB, et al. Outcomes of cervical cancer among HIV-infected and HIV-uninfected women treated at the Brazilian National Institute of Cancer. Aids. 2017;31: 523-531.

Figure 1. Association between HIV positivity and Patient Mortality, by Cancer type



Triangle: Original Hazard Ratio Estimate
Circle: Estimate in those with Private Insurance
Square: Estimate in those with Medicaid
Diamond: Estimate in those with Medicare

*oral cavity+pharynx+larynx

cncr_32158_f1.tif