Disparities and determinants of cancer treatment in elderly Americans living with HIV/AIDS

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Running title

Cancer treatment in elderly Americans with HIV

Summary

The larger differences seen in cancer treatment rates in younger individuals (≤70 years) with HIV, who may benefit the most from curative treatment in terms of added life expectancy, emphasizes the need for improved guidance and clinical intervention.

Abstract

Background: Previous studies suggest that HIV-infected cancer patients are less likely to receive cancer treatment.The extent to which this disparity affects the growing population of elderly individuals is unknown and factors that mediate these treatment differences have not been explored.

Methods: We studied 930,359 Americans aged 66-99 years old who were diagnosed with 10 common cancers. SEER-Medicare claims from 1991-2011 were used to determine HIV status and receipt of cancer treatment in 6 months following diagnosis. Mediation analysis was conducted to estimate the direct effect of HIV, and indirect effect of cancer stage at diagnosis and comorbidities, on cancer treatment.

Results: HIV-infected individuals (n=687) were less likely to receive cancer treatment (70% vs. 75% HIV-uninfected; p< 0·01). This difference was larger in individuals ≤70 years, among whom only 65% were treated (vs. 81% HIV-uninfected; p< 0·01), and time from cancer diagnosis to treatment was longer (median 42·5 vs. 36 days HIV-uninfected; p<0·01). Accounting for potential confounders, HIV-infected individuals aged ≤70 remained 20% less likely to receive cancer treatment (hazard ratio=0·81; 95% confidence interval=0·71, 0·92). Seventy-five percent of this total effect was due to HIV itself, with a nonsignificant 25% mediated by cancer stage and comorbidities.

Conclusions: The lowest cancer treatment rates were seen in the younger subset of HIV-infected individuals, who would likely benefit most from treatment in terms of life expectancy. To develop effective interventions, it is imperative to identify factors that mediate the relationship between HIV and low cancer treatment rates.

Keywords

HIV/AIDS, cancer, SEER-Medicare, chemotherapy, treatment, aging, comorbidities, inverse odds ratio weighting, mediation analysis

Introduction

Widespread and effective antiretroviral therapy (ART) has reduced the risk of developing AIDS and has greatly increased the life expectancy of HIV-infected individuals in the United States[1,2]. As such, an increasing number of HIV-infected individuals are now at risk of cancers that typically occur with aging[3]. Given the increasing burden of cancer in the aging HIV-infected population, effective strategies to treat cancer in this population are needed. It is also important to ensure that patients are being properly referred for and are receiving these treatments. Unfortunately, recent studies suggest that HIV-infected individuals are significantly less likely to receive cancer treatment compared with uninfected individuals, but findings have differed by study population and cancer type,[4,5] including one study that found that HIV-infected individuals may even be over-treated for prostate cancer[6]. Although the incidence of many cancers increases with aging, studies that focus on treatment in elderly individuals with HIV are limited to only lung cancer[5,7].

Understanding the effect of HIV on receipt of cancer treatment and identifying characteristics of HIV-infected individuals who do not receive timely and appropriate treatment are critical steps towards reducing the higher cancer-specific mortality reported for HIV-infected cancer patients [8,9]. It remains unclear the extent to which time from cancer diagnosis to initiation of cancer treatment differs between HIV-infected and uninfected individuals, and research is needed to that examine underlying drivers of HIV-related differences. For example, we hypothesize that HIV-infected individuals may be less likely to receive treatment because of competing medical conditions (comorbidities) or late stage diagnosis, where harms of treatment may outweigh benefits. In this study, we focus on a growing subset of the HIV population in America—those who are age 65 years or older and diagnosed with cancer—to examine factors associated with receipt of cancer treatment and delays in initiation of cancer therapy.

Methods

We conducted a retrospective cohort study of 930,359 older Americans in the SEER-Medicare linkage database from 1991-2012, which includes individuals diagnosed with cancer in the Surveillance, Epidemiology, and End Results (SEER) program who have been matched with their Medicare enrollment and billing claims records. The study goal was to focus on a diverse set of cancers, so we included the most common cancers in this elderly population (prostate, lung, breast, colorectal cancers), and also included both AIDS-defining (non-Hodgkin lymphoma [NHL] and non-AIDS defining cancers that are relatively common in HIV-infected individuals (cancer

of the anus, bladder, kidney, and liver, and melanoma). This study was restricted to invasive cancers that were diagnosed: (1) at ≥66 years of age to ensure at least one year of previous claims data; (2) on/after 01/1992, when both the SEER and Medicare data were available, (3) before 12/2011 to ensure one year of follow-up available after cancer diagnosis; and (4) among individuals with part A, part B, non-HMO coverage for at least one year before through one year after cancer diagnosis.

Cancer cases were defined as HIV-infected if an International Classification of Diseases (ICD)-9 code for HIV (042, 043, 044 or V08) was found in the Medicare Provider Analysis and Review (MEDPAR) file, or if 2 or more claims for those diagnosis codes were included in National Claims History (NCH) or the Outpatient files ≥30 days apart. If these criteria were not met up 365 days after the date of cancer diagnosis, cancer cases were considered HIV-uninfected.

The study outcome, receipt of initial cancer treatment, was defined as one or any combination of surgery, radiotherapy, chemotherapy including oral prescriptions, hormone/biologic therapy, or transplant within 6 months of cancer diagnosis. Cancer treatment data were ascertained using the NCH, Outpatient, MEDPAR, and durable medical equipment (DME, which contains data on oral chemotherapy) files of the SEER-Medicare linkage. For each cancer type, these files were searched for codes that indicate possible cancer treatments. Then, the final code list was compared against the National Comprehensive Cancer Network (NCCN) guidelines to ensure it included all standard treatments[10] and was further reviewed for completeness by an oncologist with expertise in using large databases to examine cancer treatment (G.S.).

Available covariates of interest in this study included age, sex, race, year of cancer diagnosis, metropolitan setting (big metropolitan /metropolitan vs. urban/less urban/rural), cancer stage, comorbidities, and socioeconomic status. To avoid collinearity and best capture SES in regression models, a composite binary variable was created based on zip code level median income, percent of high-school graduates, and percent of residents living below poverty. For prevalent comorbidities, the Medicare claims were searched for codes indicating the 15 other comorbidities (excluding cancer and HIV) included in the Charlson Index in the year prior to cancer diagnosis[11].

Statistical analysis

Demographic, clinical and health characteristics of the study population, as well as the proportion of cancer cases receiving treatment within 6 months of cancer diagnosis, were described. Pearson's Chi-squared tests and Wilcoxon rank-sum tests were used to compare these characteristics by HIV status for categorical and continuous variables, respectively; trend tests were used for ordered variables. Time from cancer diagnosis to treatment was compared by HIV status and age using Kaplan-Meier curves. Only the month and year of cancer diagnosis were available in SEER, so the date of diagnosis was assumed to be the 15th of the month. If the treatment date occurred within 15 days before the diagnosis date, we assumed they occurred at the same time.

Time-to-event analyses were used to formally compare receipt of cancer treatment by HIV status for each cancer-type, and for all cancers combined with adjustment for cancer type. In the absence of treatment, participants were censored at the earliest of death or 183 days (6 months) after cancer diagnosis. Likelihood ratio tests were used to identify potential interactions between HIV and other covariates on time to treatment. A significant interaction was found for age ($p<0{\cdot}05$), so results are stratified by age 66-70 years (younger subset) and age >70 (older subset).

Mediation analysis, using the Inverse Odds Ratio Weighting (IORW) method,[12] was employed to examine the extent to which cancer stage and comorbidities could explain the association between HIV and cancer treatment (Online supplement 1). Here, $HR_{TOTAL} = HR_{DIRECT} \times HR_{INDIRECT}$, where HRs correspond to hazard ratios for cancer treatment. HR_{TOTAL} is the estimate of the overall association (all sources and pathways) between HIV and cancer treatment, after adjustment for measured confounding factors (race, gender, composite SES, year of diagnosis (Online Supplement 2), and metropolitan setting). $HR_{INDIRECT}$ captures the "indirect" effect, which is the portion of the association between HIV and cancer treatment that is mediated, or accounted for, by differences in cancer stage and comorbidities. HR_{DIRECT} estimates the direct effect of HIV itself, that is, the portion that does not work through other cancer stage and comorbidities, although this direct effect might be mediated through other unmeasured pathways. Models were bootstrapped 500 times to estimate the standard errors. Finally, factors associated with receipt of cancer treatment among HIV-infected individuals were examined using standard Cox proportional hazards models restricted to the HIV subpopulation. Analyses were conducted using Stata v14 and R v3.3.1.

Results

In this study of elderly Americans with cancer (n=930,359), 687 were HIV-infected (0·07%), of whom the majority (n=631) had their first HIV claim prior to cancer diagnosis (median 1,281 days; IQR 660-2144; **Table 1**). Of the cancers examined, lung and prostate were the most common in both HIV-infected and uninfected individuals. HIV-infected individuals had lower proportions of bladder, breast, and colorectal cancers and higher proportions of anal, liver, and NHL, as compared to HIV-uninfected individuals. HIV-infected cancer patients were younger (median 71 years; IQR: 68-76) than HIV-uninfected patients (75; 71-81), and a higher proportion of HIV-infected individuals were non-Hispanic black or Hispanic (31% and 11%, vs. 8% and 5% in HIV-uninfected, respectively). Annual cancer screening, excluding the year before diagnosis, was higher in HIV-infected individuals (median: 0.47 screens per year vs. 0.35 in HIV-uninfected). Diagnosis of distant stage cancers was equally common by HIV status (20%), whereas HIV-infected individuals were less likely to have localized/regional cancers and more likely to have unknown stage (18% vs. 14% in HIV-uninfected). HIV-infected individuals were more likely to have a high number of comorbidities (26% had ≥4 comorbidities vs. 11% in HIV-uninfected) and to reside in metropolitan areas and areas of lower SES.

Overall, 68% of HIV-infected and 75% of HIV-uninfected individuals received cancer treatment within 6 months of cancer diagnosis ($p<0·01$). However, the differences were actually restricted to individuals aged 66-70 years: only 65% of HIV-infected individuals received cancer treatment compared to 81% of HIV-uninfected individuals ($p<0·01$; **Table 2; Figure 1**). Time from cancer diagnois to treatment initiation was also longer in HIV-infected individuals overall, but particularly among the younger subpopulation, with a median of 43 days to first treatment compared to 36 days in HIV-uninfected ($p<0·01$). The negative association between HIV and cancer treatment was also related to the type of cancer in the younger subpopulation: HIV-infected individuals were significantly less likely to be treated for colorectal, kidney, lung and prostate cancers ($p<0·05$). In the older subpopulation (>70 years), there were no differences between HIV-infected and uninfected individuals in receipt (71% vs. 73%, respectively) or time to treatment (median 31 vs. 30 days, respectively) except for anal cancer, for which treatment was delayed in HIV (median 61 days vs. 35 in HIV-uninfected; $p=0·02$).

There remained no difference in receipt of treatment by HIV status in the older subpopulation, even after adjustment for confounding variables (HR_{TOTAL}: 1·05; 95%CI: 0·93, 1·18; **Table 3**). In the younger subpopulation, HIV-infected individuals had a significantly lower rate of cancer treatment compared to HIV-uninfected individuals for all cancer combined even after adjustment (HR_{TOTAL}: 0·81; 95%CI: 0·70, 0·92 vs. unadjusted HR: 0·65; 95%CI: 0·57, 0·75). This 19% lower rate of cancer treatment can be apportioned into approximately 15% "direct" reduction due to HIV (HR_{DIRECT}: 0·85; 95%CI: 0·72, 0·99) plus a non-significant 5% reduction mediated by cancer stage and comorbidities ($HR_{INDIRECT}$: 0·95; 95%CI: 0·87, 1·04). Thus, comorbidities and stage at cancer diagnosis together mediated only 25% of the total effect of HIV on delayed cancer treatment (i.e., 1- $HR_{INDIRECT}$ / 1- HR_{TOTAL}), whereas the direct effect of HIV infection itself accounts for the remaining 75% of the total effect.

Among the specific cancer types, HIV-infected individuals with colorectal, lung and prostate cancers had lower rates of treatment compared to HIV-uninfected individuals (**Table 3**; HR_{TOTAL} <1·0; P<0·05), and these differences were not mediated by cancer stage and comorbidities. For example, HIV-infected individuals with colorectal cancer had a 37% lower rate of cancer treatment compared to HIV-uninfected individuals (HR_{TOTAL}: 0·63; 95%CI: 0·40, 0·98), and $HR_{INDIRECT}$ was not significantly <1·0. HIV-infected individuals with prostate cancer had a 29% lower rate (HR_{TOTAL}: 0·71; 95%CI: 0·54, 0·94), and those with lung cancer had a 27% lower rate of cancer treatment (HR_{TOTAL}: 0·73; 95%CI: 0·57, 0·93). Moreover, results for lung cancer indicated a significant direct contribution from HIV (HR_{DIRECT}: 0·73; 95%CI: 0·55, 0·97). There were no differences in treatment of anal, bladder, breast, or liver cancers, melanoma, or NHL between HIV-infected and uninfected individuals.

Among those with HIV, treatment varied considerably by cancer type: from as high as 93% for breast cancer to only 36% for liver cancer. Males, non-Hispanic blacks, younger individuals, and those diagnosed at distant or unknown stage had significantly lower rates of cancer treatment (**Table 4**). However, after mutually adjusting for all other variables, only age, prior cancer screening rate, and cancer stage were associated with cancer treatment rates. HIV-infected individuals with distant (aHR: 0·70; 95%CI: 0·53, 0·93) and unknown stage (aHR: 0·44; 95%CI: 0·29, 0·67) had at least a 30% lower rate of cancer treatment compared to individuals with local/regional cancers. Trends in cancer treatment across age indicate an increase in treatment up to age 80 years (aHR for 71-75 year olds: 1·16; 95%CI: 0·93, 1·47 and aHR 76-80 year olds: 1·27; 95%CI: 1·21, 1·36) compared with individuals 66-70 years old; the oldest individuals (≥81 years) had lower treatment rates (aHR:

0·72; 95%CI: 0·63, 0·82). Over 80% of HIV-infected cancer cases also had at least 1 other comorbidity, but there was no clear association with cancer treatment.

Discussion

Based on the limited inclusion of elderly individuals with HIV in previous research, this study explored treatment for a variety of cancer types in a cohort of nearly one million elderly Americans. We found that individuals with HIV were less likely to receive timely cancer treatment compared to those without HIV. In fact, 35% of HIV-infected individuals aged 66-70 years received no cancer treatment within 6 months of cancer diagnosis, and there were modest delays in time to treatment compared to HIV-uninfected individuals. After taking into account potential confounding variables, HIV-infected individuals still had 20% lower treatment rates overall, and treatment rates were lower specifically for HIV-infected individuals with colorectal, lung, and prostate cancer. Importantly, these less-treated cancers represent 3 of the 4 most common cancers studied in this HIV population. Two important clinical factors, cancer stage at diagnosis and burden of comorbidities, may explain 25% of the difference in cancer treatment rates. A recent study estimated that over a 5-year period, 10% of HIV-infected individuals in the United States developed cancer at age 65 or older[13] and cancer is the leading cause of non-AIDS associated death[8,9]. Thus, with the current aging of the HIV population, understanding the complexities in provision of cancer care and treatment will be essential to reduce disparities, prevent premature death, and improve quality of life.

A study using linked HIV and cancer registry in Texas found that HIV-infected individuals with lung cancer were less likely to receive cancer treatment as compared to HIV-uninfected individuals,[4] and HIV-infected individuals were at least 20% less likely to receive cancer treatment for a variety of other cancers as well[14]. In a prior study using Medicare data no differences in treatment for non-small cell lung cancer were seen by HIV status [5]. This is consistent with the present study, as no differences were seen in treatment rates considering the Medicare population as a whole, including for lung cancer. However, when we stratified our Medicare population by age, treatment disparities in the younger subset were observed, a finding consistent with the majority of prior studies that focused on relatively younger populations[4-6,14,15]. Notably, age-related treatment patterns differed by HIV status: treatment rates in HIV-infected individuals increased with age wheres treatment decreased with age in HIV-uninfected individuals. The decline in cancer treatment with age in HIV-uninfected individuals is consistent with prior studies of breast, colon, prostate, and other types of cancer treatment in the general

population[16-18]. However, the observed increase in treatment with age up to age 80 in the HIV population is a novel finding with no clear explanation. Together, these patterns highlight that age modifies the association between HIV and cancer treatment in the aging population, and may help to explain inconsistent results across other study populations.

As our study highlights, the growing problem of multimorbidity and thus need for polypharmacy is greatly amplified in the elderly HIV population with cancer[19,20]—80% of HIV-infected cancer patients in our study had at least 1 of 15 other comorbidities. We hypothesized that cancer treatment rates may be lower because of medical indication against treatment, perceived low benefit to harm ratio, or competing health risks. Therefore, unlike prior research, we considered factors such as comorbidities and stage at diagnosis as mediators, rather than confounders, of the association between HIV status and receipt of cancer treatment. Although cancer stage at diagnosis was an important predictor of treatment among those with HIV, there was no consistent association between comorbidity score and cancer treatment. As such, cancer stage and medical comorbidities combined accounted for only a nonsignificant 25% of the difference in cancer treatment rates between HIV-infected and HIV-uninfected cases.

Thus, our findings suggest that HIV infection itself, which accounted for 75% of the total effect in younger cancer patients (HR_{DIRECT} in our mediation analyses), is the predominant comorbidity adversely associated with cancer treatment in individuals aged 65-70. It is also likely that the total effect attributable to HIV remains affected by unmeasured confounding such as education or health behavior, or additional mediating variables that are yet to be identified. We conducted a sensitivity analysis where we added the annual number of cancer screenings to the mediation analysis of the younger subpopulation, as a marker of access to care or differences in engagement in routine care that might affect receipt of treatment. Despite observed differences in cancer screening by HIV status, this did not change the estimates of the direct (HR: 0.84, 95% CI 0.71, 0.99) or indirect (HR: 0.96, 95% CI 0.88, 1.05) effects of HIV on cancer treatment.

Our findings of differences in treatment by HIV are consistent with findings from a recent survey of oncologists, in which approximately 20% said they would modify prescribing behavior based on HIV status[21]. In addition, the majority of providers felt sufficient clinical management guidelines were not available to aid in treatment

decision-making. These findings and the extensive literature focusing on interactions between ART and chemotherapeutics[22-24] point to a need for guidelines that support individualized cancer treatment plans, in close coordination between HIV physicians and oncologists. Prior research has shown that having multidisciplinary care teams can result in treatment rates and outcomes in HIV-infected individuals that are comparable to those without HIV[25].

Prior research in the general populations suggests that longer time from cancer diagnosis to treatment could be associated with worse outcomes in breast, colorectal, and melanoma skin cancer[26]. Factors related to delayed treatment include older age, low socioeconomic status, multiple comorbidities, non-white race/ethnicity, nonprivate health insurance, and diagnosis at a referring hospital[27-29]. The present study adds to the literature by providing evidence that HIV is also associated with treatment delays, and presents the first data on time to cancer treatment in older Americans with HIV. This is an important absolute measure to consider in addition to the overall treatment rates. Prior studies have focused on treatment delays of 15-30 days[27,28,30], so it is unclear whether our observed delay of 7 days would negatively impact patient outcomes, or simply reflects the increased time needed for treatment planning in these potentially more complicated patients with HIV/AIDS.

Unfortunately, indicators of HIV progression such as CD4 counts and HIV viral loads are not available in SEER-Medicare, and data on antiretroviral claims only started in 2007 with 50-70% Medicare part D coverage, so we could not explore the extent to which severity of HIV or ART use was associated with cancer treatment. However, in the analysis of the HIV subpopulation, we included timing of first HIV diagnostic claim relative to cancer diagnosis, which was not associated with cancer treatment. In addition, analyzing the details of complex treatment algorithms was beyond the scope of this study, so future research should address whether the types or completeness of treatment, and subsequent survival, differ by HIV status and effective ART use. A strength of this study is the population-based design, which allowed us to examine several common cancers in a representative population. Although the number of cases is small for some individual cancers, this study represents one of the largest possible samples of older HIV-infected adults with cancer, since SEER-Medicare captures more than 25% of elderly Americans[31].

The elderly HIV population is at high risk for cancer, yet there are limited data specific to cancer treatment in aging HIV populations. This study begins to fill the gaps in our knowledge with regards to cancer care disparities across a variety of cancer types and subgroups less likely to receive treatment. HIV-infected individuals differ in

many ways as compared to HIV-uninfected individuals with regards to the development and management of cancer that may ultimately affect survival. Even after accounting for many of these factors, HIV-infected individuals still had lower treatment rates for common cancers, particularly the younger subset who might benefit the most from improved cancer survival in terms of additional life expectancy. The results of this study go beyond simply quantifying these disparities and highlight the need for a multi-level evaluation of barriers to care and for multidisciplinary teams to manage these complex cases, particularly younger individuals with common cancers who currently experience low treatment rates.

Notes

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Table 1. Characteristics of the study population of elderly American cancer cases by HIV status

	Characteristic	HIV-infected N (%) or Median (IQR)	HIV-uninfected N (%) or Median (IQR)	p-value[a]
Total[b]		687 (100%)	929,672 (100%)	
Type of Cancer	Prostate	181 (26.3%)	230,382 (24.8%)	0.34
	Lung	163 (23.7%)	213,630 (23.0%)	0.64
	NHL	85 (12.4%)	67,320 (7.2%)	<0.0001
	Colorectum	75 (10.9%)	145,327 (15.6%)	0.0007
	Breast	45 (6.6%)	137,333 (14.8%)	<0.0001
	Liver	33 (4.8%)	14,103 (1.5%)	<0.0001
	Bladder	30 (4.4%)	60,538 (6.5%)	0.02
	Anus	28 (4.1%)	2,790 (0.3%)	<0.0001
	Melanoma	25 (3.6%)	29,225 (3.1%)	0.46
	Kidney	22 (3.2%)	29,024 (3.1%)	0.9
Gender	Female	153 (22.3%)	406,749 (43.8%)	<0.001
	Male	534 (77.7%)	522,923 (56.2%)	
Median age in years (IQR)		71 (68, 76)	75 (71, 81)	<0.001
Age category, years	66 to 70	321 (46.7%)	228,889 (24.6%)	<0.0001
	71 to 75	184 (26.8%)	238,222 (25.6%)	
	76 to 80	105 (15.3%)	208,559 (22.4%)	
	81 or above	77 (11.2%)	254,002 (27.3%)	
Race/Ethnicity	Non-Hispanic white	364 (53.0%)	766,995 (82.5%)	<0.001
	Non-Hispanic black	216 (31.4%)	74,716 (8.0%)	
	Hispanic	78 (11.4%)	43,735 (4.7%)	
	Other/unknown	29 (4.2%)	44,226 (4.8%)	
Year of Cancer Diagnosis	1992-1995	47 (6.8%)	125,947 (13.5%)	<0.001

	1996-2000	80 (11.6%)	137,318 (14.8%)	
	2001-2005	223 (32.5%)	306,217 (32.9%)	
	2006-2011	337 (49.1%)	360,190 (38.7%)	
Cancer Stage	Local/regional	420 (61.1%)	608,051 (65.4%)	0.006
	Distant	141 (20.5%)	190,013 (20.4%)	
	Unknown	126 (18.3%)	131,608 (14.2%)	
Timing of first HIV claim relative to cancer	Days before cancer (n=631)	1,281 (660-2144)	N/A	N/A
	Days after cancer (n=56)	74 (28-170)		
Metropolitan Area	No	37 (5.4%)	158,684 (17.1%)	<0.001
Number of cancer screenings per year		0.47 (0.00, 1.29)	0.35 (0.00, 1.07)	0.001
	Yes	650 (94.6%)	770,827 (82.9%)	
Number of comorbidities	0	140 (20.4%)	337,400 (36.3%)	<0.001
	1-2	371 (54.0%)	492,537 (53.0%)	
	4+	176 (25.6%)	99,735 (10.7%)	
Zip code-based measures of SES				
Median Income (IQR)		$41027 (31008, 54977)	$45031 (34808, 58401)	<0.001
Median % Non-highschool Grads (IQR)		19.7% (10.8, 31.9)	15.9% (10.0, 25.0)	<0.001
Median % Residents below poverty (IQR)		13.3% (6.7, 23.4)	9.0% (5.2, 15.5)	<0.001
Composite Indictor of lower SES[c]		331 (48.2%)	322,272 (34.7%)	<0.001

[a]For age, year, and comorbidities, p-values are from trend tests.

[b]Among all participants without HIV (N=945,916), 16,244 (1.72%) were missing zip code level median income information, and 15,958 (1.69%) were missing zip code level percent non-high school graduates/percent of residents living below poverty information. Among all participants with HIV (N=715), 28 (3.92%) were missing zip code level median income/percent of non-high school graduates/percent of residents living below poverty.

[c]This is a composite variable which equals 1 if a participant living in an area where 1) the median income is below the median of median income of all available areas; 2) percent of non-high school graduates is higher than the median of percent of non-high school grads of all available areas; or 3) percent of residents living below poverty is higher than the median of percent of residents living below poverty of all available areas. Otherwise this variable equals 0. If any of these

three variables is missing, this variable is missing. Among all participants without/with HIV, 16,244 and 28 participants were missing this variable, respectively.

Table 2. Cancer treatment by age, HIV infection status, and cancer type[a]

	Age 66-70 years			Age > 70 years		
	HIV-infected	**HIV-uninfected**	P value[b]	**HIV-infected**	**HIV-uninfected**	P value[b]
TOTAL						
Treated, N (%)	321 (64.8%)	228,889 (81.2%)	<0.01	366 (70.8%)	700,783 (72.7%)	0.41
Days to treatment	42.5 (24, 68.5)	36 (20, 61)	<0.01	31 (18, 58)	30 (17, 50)	0.20
Anus						
Treated, N (%)	17 (82.4%)	658 (90.3%)	0.28	11 (90.9%)	2,132 (80.5%)	0.39
Days to treatment	33 (16, 62)	36 (24, 50)	0.83	61 (40, 102)	35 (23, 50)	0.02
Bladder						
Treated, N (%)	--[c] (90.0%)	11,560 (92.5%)	0.76	20 (90.0%)	48,978 (92.0%)	0.75
Days to treatment	18 (12, 20)	17 (8, 25)	0.96	15.5 (11, 25)	16 (8, 25)	0.98
Breast						
Treated, N (%)	12 (91.7%)	34,143 (95.8%)	0.47	33 (93.9%)	103,190 (90.7%)	0.52
Days to treatment	24 (6, 44)	29 (17, 44)	0.38	26 (8, 35)	28 (16, 44)	0.09
Colorectum						
Treated, N (%)	23 (73.9%)	26,863 (90.0%)	0.01	52 (80.8%)	118,464 (84.1%)	0.51
Days to treatment	29 (15, 41)	20 (11, 30)	0.06	20.5 (13, 29)	20 (11, 30)	0.79
Kidney						
Treated, N (%)	--[c] (50.0%)	7,632 (83.6%)	<0.01	12 (66.7%)	21,392 (67.7%)	0.94
Days to treatment	48 (27, 53)	25 (13, 46)	0.21	32.5 (18, 45)	25 (14, 46)	0.60
Liver						
Treated, N (%)	18 (44.4%)	3,560 (46.4%)	0.87	15 (26.7%)	10,543 (32.7%)	0.62
Days to treatment	40 (22, 83.5)	50 (29, 79)	0.57	87.5 (27.5, 160)	48 (28, 76)	0.45
Lung						
Treated, N (%)	86 (65.1%)	52,288 (75.4%)	0.03	77 (58.4%)	161,342 (58.7%)	0.97
Days to treatment	43 (32, 66.5)	35 (22, 52)	0.01	30 (19, 54)	36 (23, 55)	0.24
Melanoma						
Treated, N (%)	--[c] (85.7%)	7,093 (88.6%)	0.81	18 (88.9%)	22,132 (86.9%)	0.80

Days to treatment	18 (14, 23)	29 (17, 44)	0.22	39 (18, 54)	29 (17, 45)	0.30
NHL						
Treated, N (%)	46 (54.4%)	13,483 (60.3%)	0.41	39 (56.4%)	53,837 (52.1%)	0.59
Days to treatment	38 (22, 57)	40 (26, 61)	0.58	34 (27, 60)	40 (26, 59)	0.90
Prostate						
Treated, N (%)	92 (62.0%)	71,609 (78.0%)	<0.01	89 (70.8%)	158,773 (68.9%)	0.70
Days to treatment	66 (43, 89)	63 (41, 90)	0.60	56 (32, 82)	49 (32, 74)	0.29

[a]Percentage of participants receiving any treatment refers to the 6 month period after diagnosis. Days to treatment refers to the median number of days (and the interquartile range) from cancer diagnosis to first treatment among those receiving any treatment.

[b]P-values were calculated using Rank-Sum test.

[c]Due to SEER-Medicare data use restrictions, entries with <11 individuals have been suppressed.

Table 3. Association between HIV status and receipt of cancer treatment, stratified by age and cancer type.

Cancer Type	Age 66-70 (N=229,210)				Age > 70 (N=701,149)
	Unadjusted HR	HR_{TOTAL}[a]	HR_{DIRECT}	$HR_{INDIRECT}$	HR_{TOTAL}[a]
TOTAL	**0.65 (0.57, 0.75)**	**0.81 (0.71, 0.92)**	**0.85 (0.72, 0.99)**	0.95 (0.87, 1.04)	1.05 (0.93, 1.18)
Anus	0.77 (0.45, 1.30)	1.08 (0.52, 2.23)	1.19 (0.57, 2.47)	0.91 (0.59, 1.40)	0.88 (0.47, 1.65)
Bladder	1.31 (0.68, 2.53)	1.32 (0.82, 2.14)	1.34 (0.74, 2.44)	0.98 (0.69, 1.41)	1.05 (0.66, 1.66)
Breast	0.99 (0.55, 1.79)	1.08 (0.50, 2.33)	0.75 (0.22, 2.56)	1.44 (0.67, 3.08)	1.37 (0.97, 1.95)
Colorectum	**0.55 (0.34, 0.88)**	**0.63 (0.40, 0.98)**	0.58 (0.32, 1.05)	1.09 (0.71, 1.68)	0.92 (0.68, 1.25)
Kidney	**0.39 (0.16, 0.93)**	0.41 (0.15, 1.12)	0.64 (0.25, 1.65)	0.64 (0.28, 1.47)	0.95 (0.47, 1.90)
Liver	1.06 (0.53, 2.12)	1.17 (0.51, 2.67)	1.18 (0.50, 2.79)	0.99 (0.59, 1.67)	0.71 (0.27, 1.90)
Lung	**0.65 (0.50, 0.85)**	**0.73 (0.57, 0.93)**	**0.73 (0.55, 0.97)**	0.99 (0.85, 1.16)	1.07 (0.80, 1.43)
Melanoma	1.25 (0.56, 2.79)	1.49 (0.50, 4.45)	2.66 (0.75, 9.45)	0.56 (0.15, 2.11)	0.98 (0.60, 1.60)
NHL	1.13 (0.76, 1.67)	1.20 (0.79, 1.83)	1.16 (0.63, 2.12)	1.03 (0.69, 1.54)	1.22 (0.80, 1.86)
Prostate	**0.65 (0.50, 0.85)**	**0.71 (0.54, 0.94)**	0.77 (0.58, 1.02)	0.93 (0.80, 1.08)	1.05 (0.82, 1.35)

[a]Inverse Odds Ratio Weighting method was used to calculate Hazard Ratios for the total (HR_{TOTAL}), direct (HR_{DIRECT}), and indirect ($HR_{INDIRECT}$) effects of HIV on time to cancer treatment. Cancer diagnosis year, gender, race/ethnicity, age (categorical), zip code level SES (composite variable), metro/not metro were modeled as confounding variables for the direct effect; stage at cancer diagnosis and number of comorbidities were modeled as mediating variables.

Table 4. Characteristics associated with receipt of cancer treatment among HIV-infected cancer patients.

		Unadjusted HR (95%CI)	Fully adjusted HR (95%CI)
Number of cancer cases		687	687
Type of Cancer	Anus	1.35 (0.86, 2.10)	1.10 (0.69, 1.77)
	Bladder	**4.41 (2.87, 6.77)**	**3.72 (2.34, 5.91)**
	Breast	**3.05 (2.12, 4.39)**	**2.05 (1.28, 3.27)**
	Colorectal	**1.86 (1.35, 2.56)**	**1.69 (1.20, 2.39)**
	Kidney	0.84 (0.47, 1.49)	0.68 (0.37, 1.25)
	Liver	**0.52 (0.29, 0.94)**	**0.50 (0.27, 0.92)**
	Lung	1.00 (ref.)	1.00 (ref.)
	Melanoma	**1.90 (1.20, 3.01)**	1.49 (0.91, 2.45)
	NHL	0.88 (0.63, 1.25)	1.42 (0.88, 2.28)
	Prostate	**0.76 (0.58, 0.99)**	**0.63 (0.47, 0.86)**
Gender	Female	1.00 (ref.)	1.00 (ref.)
	Male	**0.64 (0.52, 0.79)**	0.82 (0.62, 1.09)
Age category, years	66 to 70	1.00 (ref.)	1.00 (ref)
	71 to 75	**1.37 (1.10, 1.69)**	1.15 (0.92, 1.44)
	76 to 80	**1.41 (1.32, 1.51)**	1.24 (0.94, 1.63)
	81 or above	1.04 (0.92, 1.16)	**0.69 (0.49, 0.98)**
Race/Ethnicity	Non-Hispanic white	1.00 (ref.)	1.00 (ref.)
	Non-Hispanic black	**0.75 (0.61, 0.93)**	0.83 (0.65, 1.05)
	Hispanic	1.01 (0.75, 1.34)	1.03 (0.75, 1.40)
	Other/unknown	0.94 (0.58, 1.54)	1.22 (0.74, 2.03)
Year of Cancer Diagnosis	1992-1995	1.00 (ref.)	1.00 (ref.)
	1996-2000	**1.55 (1.00, 2.41)**	1.06 (0.67, 1.69)
	2001-2005	1.04 (0.70, 1.55)	0.78 (0.51, 1.20)
	2006-2011	1.01 (0.69, 1.48)	0.76 (0.50, 1.15)
Timing of HIV claim relative to cancer	HIV diagnosed after cancer	1.05 (0.74, 1.49)	1.17 (0.81, 1.68)
	0-1000 days before cancer	1.00 (ref.)	1.00 (ref.)
	1001-2000 days before cancer	1.11 (0.88, 1.39)	1.07 (0.85, 1.35)
	> 2000 days before cancer	1.10 (0.87, 1.39)	1.04 (0.81, 1.34)
Number of cancer screenings per year		1.01 (0.95, 1.08)	**1.08 (1.00, 1.15)**
Cancer Stage	Local/regional	1.00 (ref.)	1.00 (ref.)
	Distant	**0.77 (0.60, 0.98)**	**0.71 (0.54, 0.94)**
	Unknown	**0.54 (0.41, 0.72)**	**0.43 (0.28, 0.66)**
Metropolitan Area	No	1.00 (ref.)	1.00 (ref.)
	Yes	1.16 (0.77, 1.73)	0.98 (0.65, 1.49)
Number of Comorbidities	0	1.00 (ref.)	1.00 (ref.)
	1-3	1.11 (0.88, 1.40)	1.25 (0.98, 1.59)
	4+	0.87 (0.66, 1.15)	1.01 (0.75, 1.35)

Indictor of lower SES	No	1.00 (ref.)	1.00 (ref.)
	Yes	0.87 (0.73, 1.05)	0.88 (0.71, 1.08)

Figure legends

Figure 1. Probability of receiving cancer treatment within six months of diagnosis by age and HIV status.

Figure 1.