Clinical Infectious Diseases

MAJOR ARTICLE

Markers of immune function and survival among cancer patients with HIV in the United States: a population-based registry linkage study

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BACKGROUND: People with HIV (PWH) and cancer have greater cancer-specific mortality than patients without HIV, which may reflect effects of immunosuppression. We aimed to describe the associations between low CD4 cell counts and cancer-specific mortality in PWH with cancer.

METHODS: We used linked data from HIV and cancer registries to study 12 common cancers in PWH in 14 registries in the United States and Puerto Rico in 2008–2019. We used Cox regression to estimate hazard ratios (HRs) for the association of CD4 counts measured after cancer diagnosis (0–49, 50–99, 100-199, and 200+ CD4 cells/mm^3) with cancer-specific mortality, adjusted for demographic and cancer-related factors. We estimated 3-year cancer-specific cumulative mortality using Fine-Gray models.

RESULTS: We evaluated 12,087 PWH and cancer (the most common being non-Hodgkin lymphoma [NHL, N=2311], prostate cancer [N=1681], and Kaposi sarcoma [KS, N=1423]). Cancer-specific mortality was significantly greater for individuals with a CD4 count of 0-49 compared to 200+ cells/mm^3 for NHL (HR=1.82, 95%CI=1.30–2.53), prostate cancer (HR=3.98,

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DOI: 10.1093/cid/ciag333

95%CI=1.56–10.15), KS (HR=4.16, 95%CI=1.49–11.67), lung cancer (HR=1.69, 95%CI=1.33–2.14), colorectal cancer (HR=2.79, 95%CI=1.58–4.92), and liver cancer (HR=1.44, 95%CI=1.01–2.70). For lung cancer, those with a CD4 count of 200+ cells/mm^3 had 3-year cancer-specific cumulative mortality of 52% versus 72% for those with a CD4 count of 0–49.

CONCLUSION: Among PWH with cancer, cancer-specific mortality increased with lower CD4 counts, including for solid tumors not associated with HIV, e.g., prostate and lung cancer. These results highlight the role of immunity in control of cancer.

Key words: HIV, immunosuppression, cancer survival

Key findings: Cancer-specific mortality is elevated among those with low CD4 counts, including for solid tumors not associated with HIV including prostate, lung, and colorectal cancers.

BACKGROUND

People with human immunodeficiency virus (HIV, PWH) have an elevated incidence of certain cancers and worse survival following a cancer diagnosis compared to cancer patients without HIV.[1-8] HIV is associated with reduced cancer-specific survival (i.e., a higher risk of dying from cancer), and this association persists even after accounting for the more advanced stage at diagnosis and disparities in cancer treatment seen in PWH.[6, 9-13] Similarly, immunosuppressed solid organ transplant recipients who develop cancer have worse cancer-specific survival than patients in the general population, for a range of cancer types.[6, 10, 14] Immunosuppression is thus a plausible contributor to the decreased cancer-specific survival among cancer patients with HIV. However, no prior study has assessed markers of immune function in relation to cancer-specific survival among cancer patients with HIV.

Among PWH, HIV targets and depletes CD4-positive T-cells, leading to acquired immunodeficiency syndrome (AIDS) and loss of control of other viruses that cause cancer, such as Epstein-Barr virus (EBV, a cause of some non-Hodgkin lymphomas [NHLs] and Hodgkin lymphoma [HL]), Kaposi sarcoma herpesvirus (causing Kaposi sarcoma [KS]), and human papillomavirus (causing anogenital and oropharyngeal cancers). Among PWH engaged in primary care, the peripheral blood CD4 count is routinely assessed as a direct measure of cell-mediated immune function. Peripheral blood HIV viral load is undetectable among patients on effective antiretroviral therapy, and the presence of a detectable HIV viral load may also indicate immune dysfunction.[15]

The recent emergence of cancer immunotherapy highlights the important role that augmenting a patient's immune system can play in eliminating or controlling their cancer.[16] A major advance is the advent of immune checkpoint inhibitors (ICIs), which inactivate checkpoint proteins expressed in tumors, thereby enabling an effective antitumor T-cell response. Immunotherapies enhance immune responses against tumor neoantigens, which derive from mutated human genes or are

related to oncogenic viruses. ICI therapy has demonstrated efficacy for many advanced cancers in reducing recurrence and mortality. ICIs target specific molecules on CD8+ T-cells that regulate their activation and function,[17] but the potential role of CD4 T-cells as targets for immunotherapy is less clear.

Chemotherapy and radiation therapy suppress immune cells and lead to declines in certain lymphocyte subsets.[18] The effectiveness of ICIs suggests that, even for cancer patients treated with other modalities, the immune system may likewise be important in facilitating clinical responses and maintaining remission. If so, one might hypothesize that cancer outcomes would be affected by the presence of immune-related medical conditions such as HIV infection, and that, among PWH with cancer, cancer-specific survival would be worse with more advanced HIV disease. Additional evidence on the relationship between HIV disease markers (CD4 count, HIV viral load) and survival may thus have relevance for treating cancer patients with HIV and help clarify the role of immunity in other cancer patients.

METHODS

The HIV/AIDS Cancer Match (HACM) Study links data from cancer and HIV registries across multiple regions in the United States. Registries capture demographic characteristics, dates of diagnosis, and cause of death. We included people with cancers identified by cancer registries who had HIV infection at the time of diagnosis, based on linkage to an HIV registry with an HIV report date before the cancer diagnosis date. The study was approved by institutional review boards at participating registries and was exempt from review at the US National Institutes of Health. Consent of participants was not required for the use of data collected through public health surveillance.

Cancer diagnoses were restricted to calendar years for which both the linked cancer and HIV registries provided complete ascertainment within that region. We further restricted to calendar years in which the number of CD4 and viral load results available in the HIV registry was at least 50% of that in the year when the greatest number of laboratory measures were reported and when, among PWH with a CD4 measure, at least 50% of measurements were greater than 200 cells/mm^3. These criteria aimed to reduce the potential impact of bias arising from incomplete ascertainment of CD4 counts and differential ascertainment only of CD4 counts in the presence of AIDS. We thus included cancer patients diagnosed and followed for survival in the following states/regions (calendar periods): Colorado (2011-2017), Connecticut (2008-2018), Washington, D.C. (2009-2017), Florida (2011-2019), Georgia (2010-2015), Louisiana (2009-2019), Maryland (2012-2019), Michigan (2007-2018), North Carolina (2009-2017), New Jersey (2007-2015), New York (2008-2019), Puerto Rico (2014-2019), Texas (2010-2018).

We further restricted the study to PWH age 20 to 85 years-old at their cancer diagnosis and who had a CD4 count measurement within the first three months following cancer diagnosis. Cancers

were classified based on a modified version of the Surveillance, Epidemiology, and End Results (SEER) recode.[19] We then included PWH who were diagnosed with a first cancer diagnosis (regardless whether they later developed another cancer), and restricted to the following 12 cancer sites, which were the most common: NHL, prostate, KS, lung, anus, colorectum, female breast, HL, liver, oral cavity and pharynx, kidney, and cervix.

Underlying cause of death were captured by cancer registries from death certificates, and cancer-specific deaths were defined using a modified version of the SEER cause of death recode, including some deaths mistakenly attributed to other cancers or related conditions.[19] The SEER cause of death algorithm classifies some deaths from AIDS and cancer, or AIDS alone as deaths from cancer. Because all people in our study had HIV infection, and death from AIDS might not be related to their cancer, we removed the above categories from the list of diagnoses that were recoded as cancer deaths. **Supplementary Table 1** presents the number of deaths within each cancer type were due to AIDS and cancer or AIDS alone, and which were reclassified by us as not cancer-specific. Some HIV registries participating in the HACM Study provided CD4 counts in categories rather than as specific numeric values. We therefore created a harmonized set of CD4 count categories for analysis: 0–49, 50–99, 100–199, and 200+ cells/mm^3. The category of 200+ cells/mm^3 was determined after we evaluated cancer-specific survival for categories of 300–399, 400–499, and 500+ cells/mm^3 and found that they were not statistically different from that of 200–299 cells/mm^3; collapsing these categories increased our ability to detect statistically significant differences in comparison with lower categories of CD4 counts. Similarly, HIV viral load was uniformly dichotomized as undetectable vs. detectable using a threshold of 50 copies/mL to harmonize registry reporting.

We analyzed data for each cancer type separately. From the HIV registries, we captured the latest CD4 count and HIV viral load values measured within the 3-month period after cancer diagnosis. We considered using instead CD4 count closest to cancer diagnosis, and while general findings were similar to those for the latest timepoint (data not shown), we felt that the CD4 count closest to the landmark and start of follow-up would be the most clinically meaningful. The use of a CD4 count at this timepoint was intended to capture a clinically relevant time window and, to some extent, the effects of cancer treatment in causing subsequent immunosuppression as the first line of therapy would likely have already been initiated. We then conducted a survival analysis with follow-up starting at 3 months after cancer diagnosis; individuals who died within the first 3 months were excluded.[20]

Supplementary Figure 1 describes the number of people who met these inclusion criteria according to cancer site. In our study, the proportion of patients who had at least one measure of CD4 count prior to their cancer diagnosis but did not have a measure within 3 months after varied by cancer type, ranging from 25% of patients with kidney cancer to 54% for those with prostate cancer. We excluded patients with a missing CD4 count because of a lack of clinical interpretation or relevance. Patients who died before the 3-month landmark were significantly more likely to have advanced stages of cancer. For example, 82% of patients with lung cancer who did not survive

to 3 months from cancer diagnosis had distant stage cancer compared to 50% among those who were included in the analysis. Follow-up ended at death, end of registry coverage or 3 years from cancer diagnosis, whichever occurred first.

We examined log-log survival plots for proportionality for all cancers and did not visually observe violations of the assumption. We then used Cox regression to hazards ratios (HR) for the associations of CD4 count categories with cancer-specific and overall mortality, adjusted for demographic characteristics, cancer stage, and initial cancer treatment (surgery, radiation, and chemotherapy). For prostate and breast cancers we also adjusted for reported use of hormone therapy as first course therapy. We conducted similar analyses for associations with HIV viral load with adjustment for CD4 count, subsetting the analysis to PWH with a measure of viral load during the first 3 months following their cancer. We also investigated whether the associations with CD4 count varied based on receipt of chemotherapy, focusing on lung cancer since it had the highest mortality and approximately half (52.4%) of individuals received chemotherapy. We conducted sensitivity analyses to test for an interaction between CD4 count and chemotherapy and provide HR estimates for the association between CD4 count and cancer-specific mortality stratified by reported receipt of chemotherapy.

Finally, we estimated the cumulative cancer specific mortality, i.e., the probability of cancer specific mortality in the presence of competing mortality, within 3 years from diagnosis using Fine-Gray models[21] and Nelson-Aalen curves using the cuminc function in the tidycmprsk package in R (R version 4.5.1, http://www.r-project.org).[22] We used a p-value threshold of <0.05 for statistical significance.

RESULTS

We included 12,087 PWH with cancer who survived at least 3 months from their cancer diagnosis date and had at least one CD4 count measured within that time. Among these patients, 76% were male, the median age was 53 years at cancer diagnosis, 42% were non-Hispanic Black individuals, and 25% were Hispanic individuals (**Table 1**). Stage at cancer diagnosis was localized in 41% of patients and distant in 27%, and individuals in the lowest CD4 count category were more likely to have regional or distant stage cancers than those in the highest category. One-third of included patients did not have HIV viral load available for analysis; among those with a measurement, 84% of the viral loads were undetectable.

As shown in **Table 1**, among the 1,380 individuals with CD4 counts of 0-49 cells/mm^3, 63% were younger than 50 years of age, NHL and KS were the most common cancers (33% and 29%, respectively), and 33% had distant stage cancer at diagnosis; among those with a viral load measurement, 54% were undetectable. In comparison, among the 7,688 individuals with a CD4 count of cancer of 200+ cells/mm^3, 30% were younger than 50 years, prostate cancer and NHL were the most common cancers (20% and 13%, respectively), and 46% were diagnosed with

localized stage cancer. Among the patients in this group with a viral load measurement, 91% were undetectable.

Overall, 5,001 (41.1%) people with HIV and cancer died during the follow-up period. **Table 2** shows associations of CD4 count and HIV viral load with overall mortality for each cancer type. There were significant trends for decreasing CD4 count categories and increasing overall mortality for all cancers except kidney and cervical cancers. After accounting for CD4 count, the presence of a detectable viral load was associated with greater overall mortality only for anal cancer (HR= 1.53, 95%CI=1.13–2.05).

Of the 5,001 deaths following a cancer diagnosis, 2,351 (47%) were due to cancer. **Table 3** presents the associations with cancer-specific mortality. There were significant trends in cancer-specific mortality across CD4 count categories for NHL, KS, and cancers of the prostate, lung, colorectum, and oral cavity and pharynx. A detectable viral load was associated with higher cancer-specific mortality only for KS (HR=3.44, 95%CI=1.05–11.20).

In an additional analysis for lung cancer, we stratified individuals according to whether they received chemotherapy. Among those who received chemotherapy, overall mortality was 52% higher among those with a CD4 count of 0-49 vs. 200+ cells/mm^3 (HR 1.52, 95%CI=1.11–2.10), while it was 95% higher for the same comparison among those who were not known to receive chemotherapy (HR 1.95, 95%CI=1.34–2.82). These HRs did not differ significantly from one another (p-interaction=0.20).

Figure 1 depicts estimates of 3-year cumulative overall and cancer-specific mortality. With the exception of kidney cancer, overall mortality differed significantly by CD4 count categories for all cancers, e.g., NHL (52% vs. 28% for PWH with CD4 counts of 0–49 vs. 200+ cells/mm^3), KS (42% vs. 9%), and lung cancer (90% vs. 69%). Across all CD4 count categories, the greatest 3-year cancer-specific mortality was observed for patients with cancers of the lung, liver, colorectum, and oral cavity and pharynx. Lung cancer was the only cancer for which cancer-specific mortality was at least 50% for all CD4 count categories. Among PWH with lung cancer, the median cancer-specific survival was 700 days for those with a CD4 count of 200+ cells/mm^3 vs. 334 days for those with a CD4 of 0-49 cells/mm^3. We also note that in a comparison of people with lung cancer according to CD4 count category, there were no significant differences in age, stage at cancer diagnosis, or overall cancer treatment. Nelson-Aalen curves showing cancer-specific survival according to CD4 count are in **Supplementary Figures 2 A–L**.

DISCUSSION

We found that CD4 counts following a cancer diagnosis were strongly associated with survival outcomes among PWH for many of the most common cancers in this population. While it is not surprising that low CD4 counts are associated with increased overall mortality (due to deaths from

AIDS), we show that low CD4 counts are also strongly associated with cancer-specific mortality. We found strong associations for lung cancer, which is the second largest cause of cancer mortality in PWH,[23] with nearly a year difference in median cancer-specific survival between the highest and lowest CD4 categories. The lowest CD4 count category was associated with increased cancer-specific mortality for NHL and KS, for which deaths are infrequently attributed to the cancer diagnosis itself.[24, 25] We also found strong associations between immunosuppression and cancer-specific mortality for prostate and colorectal cancers, which are common but not associated with HIV infection.[24]

Only a single study has assessed CD4 count and HIV viral load measurements as predictors of survival among cancer patients with HIV.[8] That study showed that a low CD4 count was an independent predictor of decreased overall survival. However, the study included only 196 PWH diagnosed with diverse cancer types, and because it assessed only overall survival, the associations with CD4 count partly reflected deaths from AIDS. In the present study, we showed that cancer-specific mortality was higher among PWH with lower CD4 counts for KS, NHL, lung cancer, colorectal cancer, and prostate cancer, suggesting that some deaths in this population can be attributed to impaired immune surveillance of cancer. Our data on HIV viral load were more limited, but we saw an adverse association of detectable HIV viral loads with increased cancer-specific mortality for KS. The lack of other associations with HIV viral load was also found in the prior study[8]. It is possible that viral suppression is more strongly predictive of survival in the immediate period after cancer diagnosis, and that those PWH with a detectable viral load were less likely to survive to enter our study follow-up at the 3-month timepoint.

Radiotherapy and chemotherapy are known to result in decreases in CD4 count. In addition to adjusting for these treatments in our analysis, we used of a 3-month landmark analysis that likely captured some of the effects of the first course of cancer treatment in causing an initial decline in CD4 cells. Calkins et al. found that among PWH with cancer who had a baseline CD4 count of greater than 500 cells/mm^3, chemotherapy and/or radiotherapy decreased initial CD4 count by approximately 200 cells/mm^3 within one week of initiating treatment.[8] In our primary analyses, we adjusted for receipt of cancer-directed surgery, radiotherapy, and chemotherapy to estimate the associations of CD4 count and survival independent of the effects of cancer treatment. We also conducted an analysis for lung cancer patients stratified according to receipt of chemotherapy, as lung cancer exhibited the highest mortality and there was substantial variation in receipt of chemotherarpy. Importantly, we did not find evidence that the association between CD4 and cancer-specific mortality differed between lung cancer patients who did vs. did not receive chemotherapy. However, we note that treatment is known to be underascertained by cancer registries.[26]

Our study has several strengths. It is population-based, including PWH from multiple US regions, and its large size allowed us to analyze different cancer types separately. Notably, the information on cause of death allowed us to evaluate cancer-specific mortality in addition to overall mortality (which is impacted by deaths due to AIDS). Nevertheless, we acknowledge some limitations. CD4

counts and HIV viral load measurements may not have been completely and systematically reported to HIV registries, which would limit how we could assess these markers. We conducted a landmark analysis using measurements from the first 3 months after cancer diagnosis, which excluded people who died before that timepoint. However, prior work has shown CD4 counts to be fairly stable after 3 months from initiating treatment.[8] We lacked data on antiretroviral therapy regimens and adherence, although the effects of HIV treatment in the initial 3-month period after cancer diagnosis would have been captured to some extent by the CD4 count and HIV viral load. We also lacked data on additional risk factors that could impact survival, such as smoking, medical comorbidities, and specific cancer treatments. Although these would need to be strongly related to cancer-specific survival and CD4 counts to affect our results, residual confounding cannot be ruled out. In addition, we note that, for a person with an HIV-related cancer (e.g., KS or NHL) who also had advanced HIV disease, there could have been diagnostic confusion whether they died from their cancer or from AIDS, which could have led clinicians to over-report or under-report cancer as the underlying cause of death on the death certificate. For other cancers unrelated to HIV (e.g., breast or prostate cancer), such misclassification would likely be much lower. Indeed, we observed that over half of all deaths among people with NHL were coded as due to AIDS and cancer or AIDS alone (this proportion was much smaller for cancers not associated with HIV [e.g., 4% for breast and prostate cancer patients])). We used a conservative approach to defining cancer-specific death by removing such deaths, which we believe better captures deaths due to progression of the rather than progression of HIV disease. Finally, we also acknowledge that our interpretation of statistical significance did not account for multiple testing but note that nearly all significant results had p-values <0.001.

ICIs are increasingly used for treatment of advanced cancers, including colorectal and lung cancers. ICIs augment antitumor CD8 T-cell responses by targeting regulatory proteins, such as programmed cell death 1 (PD-1) and cytotoxic T-lymphocyte associated protein 4 (CTLA4), that inhibit CD8 T-cell activation.[27] Our findings regarding the association between CD4 count and cancer-specific mortality among PWH highlight the additional role of CD4 T-cells in control of cancer. CD4 T-cells have important antitumor functions, including inhibition of tumor growth through production of cytokines (e.g., interferon-γ and inteferon-α), enhancing cytotoxicity and longevity of CD8 T-cells, and activating innate immune cells.[28] Indeed, approaches for activating CD4 T-cells are being considered for immunotherapy.[28]

Cancer is a leading cause of death among PWH, and the poor survival among PWH with cancer cannot be entirely explained by an advanced stage at diagnosis or inadequate cancer treatment.[9, 11] Our results highlight the likely role of HIV-related immunodeficiency in adversely affecting cancer outcomes, including for prostate, lung, and colorectal cancers, which are projected to become three of the most common cancers in PWH and which contribute substantially to excess mortality.[29, 30] Our findings highlight the importance of prompt antiretroviral therapy for those PWH with cancer not already receiving it, which will help boost CD4 counts and potentially

augment antitumor immunity. Clinical guidelines also stress the importance of administration of appropriate cancer treatments and monitoring CD4 counts throughout the course of therapy.[31]

Data sharing

The data used in this article cannot be shared publicly due to the terms of the National Cancer Institute's data use agreements with the cancer and HIV surveillance systems.

Role of the Funding Source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report, but did review a final version of the manuscript prior to submission.

Acknowledgements & Sources of Funding:

This research was supported [in part] by the Intramural Research Program of the National Institutes of Health (NIH). The contributions of the NIH author(s) were made as part of their official duties as NIH federal employees, are in compliance with agency policy requirements, and are considered Works of the United States Government. However, the findings and conclusions presented in this paper are those of the author(s) and do not necessarily reflect the views of the NIH or the U.S. Department of Health and Human Services.

The authors gratefully acknowledge the support and assistance provided by individuals at the following state HIV/AIDS and cancer registries: Colorado, Connecticut, District of Columbia, Florida, Georgia, Louisiana, Maryland, Massachusetts, Michigan, New Jersey, New York, North Carolina, Puerto Rico, and Texas. We also thank Timothy McNeel at Information Management Services for programming support. Dr. Cameron B. Haas had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The views expressed in this paper are those of the authors and should not be interpreted to reflect the views or official policies of the National Cancer Institute, Centers for Disease Control and Prevention or the Department of Health and Human Services, HIV/AIDS or cancer registries, or their contractors, nor does the mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government. This research was supported in part by the Intramural Research Program of the National Cancer Institute.

The following cancer registries were supported by the cooperative agreement funded by the Centers for Disease Control and Prevention, National Program of Cancer Registries: Colorado (NU58DP006347-01), Georgia (5U58DP003875-01), Florida (NU58DP007161), Louisiana (NU58DP006332-03-00), Maryland (NU58DP007114), Massachusetts (NU58DP006271-04-00), Michigan (17NU58DP006334), New Jersey (NU58DP007117), New York (6NU58/DP006309), North Carolina (1NU58DP006281), Texas (1NU58DP0063085NU58DP006308-04-00). District

of Columbia is supported by the Centers for Disease Control and Prevention cooperative agreement DP006302.

The following cancer registries were supported by the SEER Program of the National Cancer Institute: Connecticut (HHSN261201300019I), Louisiana (HHSN261201800007I/ HHSN26100002), Massachusetts (HHSN2612018000081), New Jersey (75N91021D00009), and New York (HHSN261201800009I). The New Jersey State Cancer Registry was also supported by the state of New Jersey and the Rutgers Cancer Institute, the Maryland Cancer Registry was supported by the State of Maryland and the Maryland Cigarette Restitution Fund, the Louisiana Tumor Registry was also supported by the state of Louisiana (0587200015), and the New York State Cancer Registry was also supported by the state of New York.

The following HIV registries were supported by HIV Incidence and Case Surveillance Branch of the Centers for Disease Control and Prevention, National HIV Surveillance Systems: Colorado (NU62PS003960), Connecticut (5U62PS001005-05), Florida (NU62PS924532), Louisiana (NU62PS924522-02-00), Michigan (U62PS004011-02), New Jersey (U62PS004001-2), New York (NU62PS924546-02-00; PS18-1802: Integrated HIV Surveillance and Prevention Programs for Health Departments, National Center for HIV, Viral Hepatitis, STD, and TB Prevention (NCHHSTP).

Data Availability

NCI cannot release individual level data to anyone outside of NCI according todata use agreements. Interested investigators can access data from individual state (or region) linkages by obtaining approval directly from the HIV and cancer registries in those states. In addition, collaboration between outside investigators and the NCI is possible.

Declaration of interests

All authors state that they have nothing to disclose.

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Table 1. Demographic and clinical characteristics of people with HIV and cancer, overall and according to CD4 count measured within the first 3 months after cancer diagnosis.

		CD4 count in the first 3 months after cancer diagnosis, cells/mm^3			
	Overall	0-49	50-99	100-199	200+
Total	12087	1380	965	2054	7688
Male sex	9198 (76.1)	1056 (76.5)	766 (79.4)	1615 (78.6)	5761 (74.9)
Age at cancer diagnosis (years)					
20-29	576 (4.8)	150 (10.9)	74 (7.7)	122 (5.9)	230 (3.0)
30-39	1301 (10.8)	292 (21.2)	156 (16.2)	288 (14.0)	565 (7.3)
40-49	2862 (23.7)	426 (30.9)	320 (33.2)	587 (28.6)	1529 (19.9)
50-59	4295 (35.5)	371 (26.9)	305 (31.6)	692 (33.7)	2927 (38.1)
60-69	2429 (20.1)	118 (8.6)	88 (9.1)	302 (14.7)	1921 (25.0)
70+	624 (5.2)	23 (1.7)	22 (2.3)	63 (3.1)	516 (6.7)
Race/ethnicity					
Hispanic	3018 (25.0)	409 (29.6)	255 (26.4)	509 (24.8)	1845 (24.0)
Non-Hispanic Black	5247 (43.4)	647 (46.9)	408 (42.3)	868 (42.3)	3324 (43.2)
Non-Hispanic White	2901 (24.0)	220 (15.9)	226 (23.4)	515 (25.1)	1940 (25.2)

Unknown/other	921 (7.6)	104 (7.5)	76 (7.9)	162 (7.9)	579 (7.5)
Cancer site					
Non-Hodgkin lymphoma	2311 (19.1)	462 (33.5)	300 (31.1)	534 (26.0)	1015 (13.2)
Prostate	1681 (13.9)	30 (2.2)	31 (3.2)	116 (5.6)	1504 (19.6)
Kaposi sarcoma	1423 (11.8)	400 (29.0)	207 (21.5)	313 (15.2)	503 (6.5)
Lung	1407 (11.6)	112 (8.1)	90 (9.3)	240 (11.7)	965 (12.6)
Anus	1248 (10.3)	136 (9.9)	120 (12.4)	261 (12.7)	731 (9.5)
Colorectum	763 (6.3)	27 (2.0)	31 (3.2)	104 (5.1)	601 (7.8)
Female breast	698 (5.8)	17 (1.2)	18 (1.9)	46 (2.2)	617 (8.0)
Hodgkin lymphoma	666 (5.5)	75 (5.4)	59 (6.1)	165 (8.0)	367 (4.8)
Oral cavity and pharynx	626 (5.2)	39 (2.8)	48 (5.0)	102 (5.0)	437 (5.7)
Liver	625 (5.2)	31 (2.2)	31 (3.2)	88 (4.3)	475 (6.2)
Kidney	339 (2.8)	15 (1.1)	5 (0.5)	31 (1.5)	288 (3.7)
Cervix	300 (2.5)	36 (2.6)	25 (2.6)	54 (2.6)	185 (2.4)
Cancer stage at diagnosis					
Localized	4909 (40.6)	439 (31.8)	272 (28.2)	658 (32.0)	3540 (46.0)
Regional	2832 (23.4)	299 (21.7)	242 (25.1)	479 (23.3)	1812 (23.6)
Distant	3224 (26.7)	464 (33.6)	337 (34.9)	710 (34.6)	1713 (22.3)
Unstaged/missing	1122 (9.3)	178 (12.9)	114 (11.8)	207 (10.1)	623 (8.1)
*Initial cancer treatment					
Surgery	4225 (35.0)	281 (20.4)	219 (22.7)	519 (25.3)	3206 (41.7)
Radiation	3564 (29.5)	330 (23.9)	273 (28.3)	593 (28.9)	2368 (30.8)
Chemotherapy	5941 (49.2)	790 (57.2)	582 (60.3)	1225 (59.6)	3344 (43.5)
HIV viral load					
Undetectable	6816 (84.1)	371 (54.2)	379 (65.9)	971 (76.6)	5095 (91.3)
Detectable	1291 (15.9)	314 (45.8)	196 (34.1)	296 (23.4)	485 (8.7)
Missing**	3980	695	390	787	2108
Year of cancer diagnosis					
2006-2012	4506 (37.3)	652 (47.2)	404 (41.9)	818 (39.8)	2632 (34.2)
2013-2019	7581 (62.7)	728 (52.8)	561 (58.1)	1236 (60.2)	5056 (65.8)

All entries are N (%). *Individuals may have received more than one modality of treatment, so the column percentages do not total 100%. **People with missing HIV viral load meausrements are excluded from analyses of HIV viral load

but retained in other analyses; thus, percentages of detectable and undetectable viral load are shown after excluding missing values.

Table 2. Associations of overall survival with CD4 count and HIV viral load measured in the first 3 months after cancer diagnosis.

Cancer type	Overall deaths	Hazard ratio (95% confidence interval [CI]) according to CD4 count					Hazard ratio (95% CI) for detectable HIV viral load
		0-49 vs. 200+ cells/mm^3	50-99 vs. 200+ cells/mm^3	100-199 vs. 200+ cells/mm^3	Per decreasing CD4 count category	p-trend for CD4 count	
Non-Hodgkin lymphoma	485	2.08** (1.77-2.44)	1.38* (1.13-1.68)	1.23* (1.04-1.46)	1.26** (1.20-1.33)	2.80e-18	1.14 (0.93–1.38)
Prostate	330	2.06* (1.19-3.57)	2.11* (1.1-4.05)	1.55* (1.08-2.21)	1.34** (1.15-1.55)	1.27e-04	1.06 (0.65–1.73)
Kaposi sarcoma	391	4.40** (3.35-5.77)	1.96** (1.38-2.79)	1.63* (1.17-2.26)	1.63** (1.50-1.78)	7.92e-29	1.32 (0.99–1.76)
Lung	1082	1.73** (1.40-2.13)	1.72** (1.36-2.17)	1.22* (1.04-1.42)	1.22** (1.15-1.30)	1.39e-10	0.95 (0.76–1.20)
Anus	518	1.52* (1.17-1.98)	1.44* (1.09-1.92)	1.47** (1.19-1.82)	1.17** (1.08-1.26)	1.21e-04	1.53 (1.13–2.05)**
Colorectum	335	2.17* (1.34-3.51)	1.00 (0.60-1.65)	1.13 (0.83-1.55)	1.18* (1.03-1.36)	1.75e-02	1.10 (0.75–1.61)
Breast	200	1.46 (0.75-2.86)	2.38* (1.26-4.49)	1.78* (1.13-2.82)	1.27* (1.07-1.51)	5.43e-03	1.36 (0.81–2.29)
Hodgkin lymphoma	166	2.07** (1.35-3.18)	1.50 (0.92-2.46)	1.42 (0.97-2.07)	1.26** (1.11-1.44)	6.14e-04	1.29 (0.73–2.29)
Oral cavity and pharynx	318	1.31 (0.88-1.97)	1.61* (1.09-2.38)	1.27 (0.95-1.70)	1.15* (1.02-1.28)	1.95e-02	1.25 (0.82–1.91)
Liver	473	1.74* (1.17-2.59)	1.42 (0.94-2.15)	1.39* (1.07-1.81)	1.22** (1.09-1.36)	3.64e-04	1.16 (0.77–1.74)

Kidney	94	1.69 (0.72-3.95)	0.65 (0.09-4.88)	1.66 (0.94-2.92)	1.20 (0.93-1.54)	1.62e-01	0.53 (0.20–1.37)
Cervix	119	1.09 (0.63-1.89)	1.13 (0.62-2.05)	1.38 (0.86-2.21)	1.04 (0.88-1.22)	6.66e-01	1.47 (0.80–2.68)

Cox regression models were adjusted for sex, race/ethnicity, cancer stage at diagnosis, and receipt of radiation, surgery, and chemotherapy. Analyses for breast and prostate cancers were additionally adjusted for hormone therapy. The model for HIV viral load excluded individuals with missing viral load measurements and was additionally adjusted for CD4 count.

*p-value<0.05

**p-value <0.01

Table 3. Associations of cancer-specific survival with CD4 count and HIV viral load measured in the first 3 months after cancer diagnosis.

Cancer type	Cancer-specific deaths	Hazard ratio (95% confidence interval [CI]) according to CD4 count					Hazard ratio (95% CI) for detectable HIV viral load
		0-49 vs. 200+ cells/mm^3	50-99 vs. 200+ cells/mm^3	100-199 vs. 200+ cells/mm^3	Per decreasing CD4 count category	p-trend	
Non-Hodgkin lymphoma	132	1.82** (1.30-2.53)	1.14 (0.75-1.75)	1.19 (0.86-1.66)	1.20* (1.07-1.34)	1.13e-03	0.76 (0.50–1.16)
Prostate	85	3.72* (1.45-9.53)	1.76 (0.41-7.47)	0.88 (0.39-2.01)	1.42* (1.04-1.92)	2.52e-02	1.03 (0.34–3.07)
Kaposi sarcoma	29	4.16* (1.49-11.67)	0.72 (0.14-3.82)	1.59 (0.47-5.35)	1.60* (1.15-2.24)	5.88e-03	3.44 (1.05–11.2)*
Lung	807	1.69** (1.33-2.14)	1.62** (1.23-2.14)	1.16 (0.96-1.39)	1.20** (1.12-1.29)	3.69e-07	0.87 (0.65–1.15)
Anus	256	1.20 (0.81-1.77)	1.45 (0.96-2.18)	1.52* (1.12-2.05)	1.10 (0.98-1.23)	9.50e-02	1.53 (0.99–2.39)
Colorectum	212	2.79** (1.58-4.92)	0.67 (0.32-1.38)	1.22 (0.83-1.80)	1.20* (1.01-1.43)	3.97e-02	0.85 (0.50–1.44)
Breast	108	1.14 (0.44-2.96)	1.10 (0.34-3.58)	1.95* (1.09-3.49)	1.13 (0.88-1.45)	3.40e-01	1.32 (0.63–2.78)
Hodgkin lymphoma	22	1.44 (0.39-5.36)	0.43 (0.05-3.43)	1.53 (0.58-4.00)	1.04 (0.69-1.58)	8.53e-01	-
Oral cavity and pharynx	187	1.00 (0.57-1.77)	1.24 (0.73-2.10)	1.04 (0.70-1.53)	1.03 (0.88-1.22)	6.66e-01	1.12 (0.61–2.09)

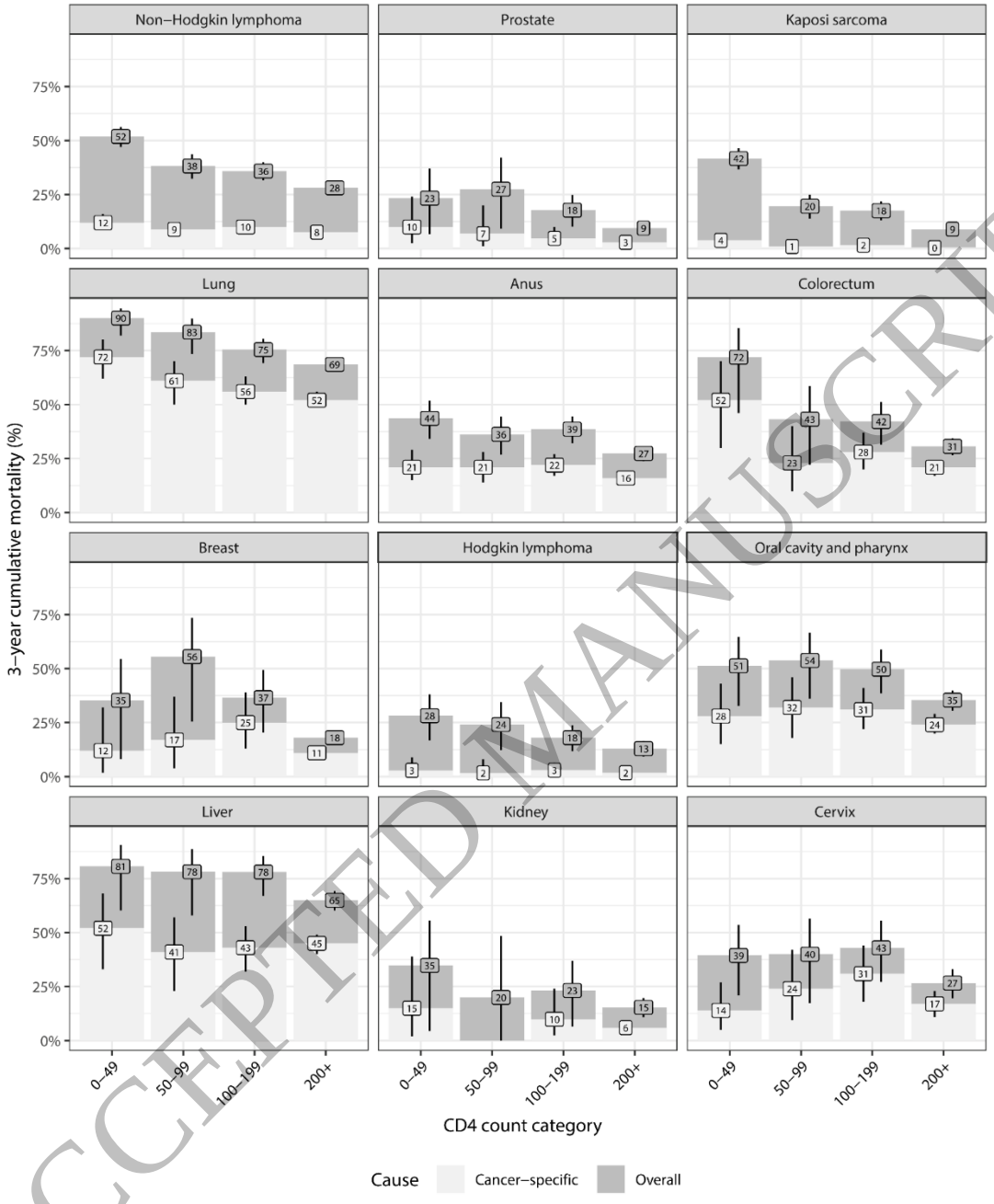
Liver	311	1.65* (1.01-2.70)	1.11 (0.63-1.97)	1.05 (0.74-1.49)	1.14 (0.98-1.31)	8.09e-02	0.78 (0.44–1.38)
Kidney	33	2.09 (0.44-9.88)	0	1.76 (0.66-4.71)	1.22 (0.76-1.94)	4.08e-01	0.20 (0.03–1.42)
Cervix	62	0.49 (0.19-1.29)	0.97 (0.43-2.18)	1.37 (0.73-2.55)	0.86 (0.67-1.10)	2.22e-01	2.29 (0.99–4.87)

Cox regression models were adjusted for sex, race/ethnicity, cancer stage at diagnosis, and receipt of radiation, surgery, and chemotherapy. Analyses for breast and prostate cancers were additionally adjusted for hormone therapy. The model for HIV viral load excluded individuals with missing viral load measurements and was additionally adjusted for CD4 count. The HR associated with detectable measures of HIV viral load could not be estimated for Hodgkin lymphoma due to zero events occurring among those with detectable levels.

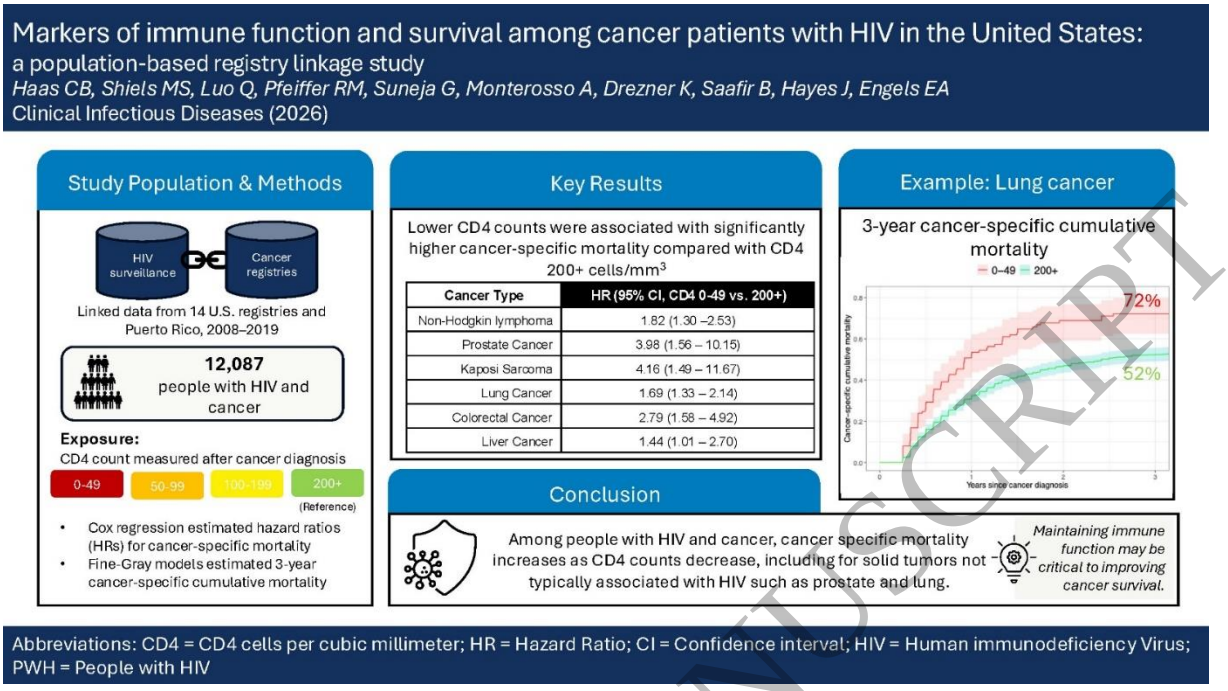
*p-value<0.05

**p-value <0.01

Figure 1. Three-year overall and cancer-specific mortality among PWH with cancer, according to CD4 count in the first 3 months after cancer diagnosis. Vertical lines correspond to 95% confidence intervals for the mortality estimates.



DOI: 10.1093/cid/ciag333



Graphical Abstract