Mortality after cancer diagnosis in HIV-infected individuals treated with antiretroviral therapy

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Objective(s): To evaluate survival and predictors of mortality after cancer diagnosis among HIV-infected persons receiving combination antiretroviral therapy (cART).

Design: Multi-site cohort study

Methods: We examined all-cause mortality among HIV-infected patients treated with cART in routine care at eight US sites and diagnosed with cancer between 1996 and 2009, and predictors of mortality using Cox proportional hazards regression models. Non-AIDS defining cancers (NADCs) were classified as related and unrelated to viral co-infections.

Results: Out of 20,677 persons in the CNICS cohort, 650 cART treated individuals developed invasive cancer. Of these, 305 died during 1,480 person-years of follow-up; crude mortality rate was 20.6 per 100 person-years (95%CI: 18.4, 23.1) and overall 2-year survival was 58% (95%CI: 54, 62%). Highest mortality was seen in primary central nervous system non-Hodgkins lymphoma, liver, and lung cancer with rates of 90.6, 84.3, and 68.1 per 100 person-years, respectively. Adjusted hazard of death was higher among those who were older and had stage IV cancer. Adjusted hazard of death was lower among those with higher CD4 cell counts at cancer diagnosis, who achieved HIV RNA suppression ($\leq$400 copies/mL) on cART, received any cancer treatment, and had AIDS-defining cancer or infection-related NADCs compared to infection-unrelated NADCs.

Conclusions: Independent predictors of mortality after cancer diagnosis among HIV-infected persons include poor immune status, failure to suppress HIV RNA on cART, cancer stage, and lack of cancer treatment. Modification of these factors with improved strategies for the prevention and treatment of HIV and HIV-associated malignancies are needed.

AIDS 2011, **25**:000–000

Keywords: antiretroviral therapy, cancer, HIV, mortality, survival

Introduction

The widespread use of combination antiretroviral therapy (cART) has led to dramatic reductions in morbidity and mortality from AIDS-related conditions for individuals infected with HIV [1,2]. However, several studies have reported an increased incidence of non-AIDS-defining cancers (NADCs) [3–14], in particular those related to

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Received: 25 August 2010; revised: 29 November 2010; accepted: 2 December 2010.

DOI:10.1097/QAD.0b013e3283437f77

ISSN 0269-9370 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins

oncogenic viral co-infections, such as human papillomavirus (HPV), Epstein-Barr virus (EBV), and hepatitis B or C virus (HBV or HCV) [8,15,16], among individuals with HIV-infection compared to the general population.

Trends in relative incidence rates of AIDS-defining cancers (ADCs) and NADCs have been well characterized [8,15–19], but little is known about survival after a diagnosis of cancer in the setting of HIV infection. Previous studies have been limited to examining individuals with AIDS in the pre-cART era or have lacked information regarding important risk factors [20–22]. We studied a large cohort of HIV-infected individuals engaged in routine care at eight clinical sites across the US to define risk factors and mortality rates after a diagnosis of cancer in the modern cART era.

Methods

Study population

The Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) was initiated in September 2006 to develop a comprehensive and standardized clinical data repository from point-of-care electronic medical record systems to support population-based HIV research [23]. The CNICS cohort includes over 20,000 HIV-infected adults (at least 18 years of age) engaged in clinical care from January 1, 1995 to the present at eight CFAR sites. The frequency of follow-up averages every 3 months, however patients can be seen more or less often depending on clinical care. CNICS is a dynamic cohort with approximately 1400 new patients enrolling and 10% of existing patients leaving care each year [23]. Institutional review boards at each University approved study protocols.

We examined all individuals in the CNICS cohort who were treated with cART for at least six months and had a diagnosis of cancer between January 1, 1996 and July 1, 2009. Follow up was administratively censored at 7 years to ensure adequate numbers of patients at risk for mortality.

Sources of data

Upon entry into the CNICS cohort, standardized demographic and historical information, including prior diagnoses and antiretroviral treatment, are collected. Once enrolled in the cohort, data are prospectively captured at outpatient and inpatient encounters at the site medical center and include medications, laboratory test results, and AIDS and non-AIDS defining conditions diagnosed by the treating provider and verified by medical record review (www.cnics.net). The following variables were included in this analysis: demographics (i.e., year of birth, sex, race/ethnicity), alcohol and tobacco exposure, intravenous drug use (IDU) as a risk factor for HIV transmission, Hepatitis B and C viral co-infection, AIDS-defining diagnoses, cART, CD4 cell counts, and plasma HIV RNA levels. Hepatitis C virus (HCV) infection was defined by positive HCV antibody or HCV RNA testing prior to cancer diagnosis. Hepatitis B virus (HBV) infection was defined by positive HBV surface antigen or HBV DNA testing prior to cancer diagnosis. CD4 cell count and HIV RNA values at the time of cancer diagnosis were the values closest to the diagnosis date within a window of nine months before and three months after cancer diagnosis. HIV RNA suppression was defined as any HIV RNA level less than or equal to 400 copies/mL after cART initiation and before cancer diagnosis. Tobacco exposure and alcohol abuse were determined at the clinical assessment closest to cancer diagnosis to be current, past or never. If there were no clinical records documenting alcohol or tobacco assessments prior to the cancer diagnosis or for six months after, the patient was classified as never exposed. Alcohol exposure was defined as abuse if qualitative assessments described "abuse", "daily", "dependence", or "binge", and if quantitative alcohol exposure was greater or equal to three drinks daily or ten drinks per week.

Cancer verification

At each CNICS site, incident diagnoses of invasive cancer were reviewed using a standardized protocol to confirm the diagnosis and collect detailed information regarding cancer type, histology, grade, staging, and treatment from the medical record. Every CNICS site used the same protocol for cancer review and data collection. Cancer types were classified according to a pre-defined grouping based on location (i.e., anal, breast, cervix, lung) and/or histopathologic reports (i.e., Kaposi sarcoma (KS), lymphoma, leukemia), non-melanoma skin cancers were not included. Histology, grade, TNM and summary staging were obtained from information provided in pathology reports and clinician notes. If a patient had more than one cancer diagnosis, we analyzed only the first cancer observed. Treatment for cancer was defined as having received at least one treatment modality regardless of timing or completion of therapy categorized as: surgery, chemotherapy, radiation, biologic, or none. Biopsy results confirmed 89% of non-KS cancers; the remaining cancers were diagnosed based on clinical, radiographic, or historical information. KS was staged as mucocutaneous or visceral based on AIDS Clinical Trials Group (ACTG) classification tumor status. Cancers qualitatively described as "metastatic", "widespread" or "disseminated" were defined as stage IV. Visceral KS and primary CNS non-Hodgkin lymphoma (NHL) were classified as "stage IV equivalent" and mucocutaneous KS was classified as "not stage IV equivalent". Cancer stage was categorized as missing/unknown if staging information was not available after careful review of medical records. To address the lack of complete data on cancer staging, we imputed missing "stage IV equivalent" information as per the methods described below for the final multivariable analysis of all cancer cases. To examine the validity of this approach, we performed two

pre-specified subset analyses in which stage of cancer was known for all cases. The first subset analysis examined cancers using the I-IV summary staging classification (excluding KS, leukemia, multiple myeloma, primary CNS NHL, and primary brain). In this subset, we ran the same multivariable analyses conducted for the full cohort of cancer cases with the variable "stage IV" or "not stage IV". For the second subset analysis, we performed the same multivariable analysis with the addition of cases categorized as "stage IV equivalent" or "not stage IV equivalent".

ADCs included cervical, KS, and NHL according to the 1993 CDC criteria [24]. NADCs were classified into those related to viral co-infections (HPV, EBV, and viral hepatitis) and those unrelated to viral co-infection. Infection-related NADCs included [16]: squamous cell anal, squamous cell oral cavity/pharynx, Hodgkin lymphoma, liver with viral hepatitis, vagina/vulva, and penis. Infection unrelated NADCs included: non-squamous cell anal, biliary, bladder/urinary, primary brain, breast, colorectal, esophagus, non-squamous cell oral cavity/pharynx, other head and neck, ovary, other (type unspecified or unknown), pancreas, kidney, leukemia, liver without viral hepatitis, lung, multiple myeloma, melanoma, peritoneum/retroperitoneum, prostate, small intestine, soft tissue, stomach, testicular, thyroid, trachea/pleura, and uterus.

Mortality ascertainment

Death data were obtained from clinic sources and confirmed by the National Death Index. In addition, the National Death Index was searched quarterly for all CNICS participants who were not known to be alive. We examined rates and predictors of all-cause mortality.

Statistical analysis

Mortality rates were calculated as number of deaths per 100 person-years of follow-up time. The complement of Kaplan-Meier survival curves were used to display the time from cancer diagnosis to death [25], as well as to estimate 2-year survival. We used Cox proportional hazards regression models to examine predictors of mortality [26]. Factors included in multivariable models were type of cancer (categorized as ADC, infection-related NADC, and infection-unrelated NADC), age, race/ethnicity, sex, viral hepatitis co-infection, current and past tobacco exposure, current and past alcohol abuse, nadir CD4 cell count, CD4 cell count at cancer diagnosis, pre-cART HIV RNA level, HIV RNA suppression on cART, non-cancer AIDS-defining diagnosis, cancer stage, cancer treatment, and year of cancer diagnosis. The assumption that continuous predictors (i.e., age at cancer diagnosis, CD4 cell count, and HIV RNA) had a log-linear association with the mortality hazard was explored and when violated the continuous predictor was categorized to reflect the non-log-linear association. The proportional hazards assumption was explored graphically by plotting the log of the cumulative hazard by time.

We imputed the median or modal value for infrequently missing variables (see Table 1, footnote B). In the final multivariable model, for cases missing "stage IV equivalent" information (see Table 4, footnote B), we

Table 1. Characteristics of 650 HIV-infected adults treated with cART in the CNICS cohort diagnosed with cancer between 1996 and 2009.

Characteristics at cancer diagnosis:[a]	Survivors	Deaths	Overall
Total, n	345	305	650
Follow-up time, years	2.8 (1.2, 5.0)	0.6 (0.2, 1.5)	1.4 (0.4, 3.7)
Age, years	43 (38, 50)	46 (40, 54)	44 (39, 51)
White, n (%)	203 (59)	137 (45)	340 (52)
Male, n (%)	293 (85)	263 (86)	556 (86)
HBV/HCV infection, n (%)	60 (17)	74 (24)	134 (21)
IDU, n (%)	49 (14)	69 (23)	118 (18)
Smoking, n (%):[b]			
Never	133 (39)	117 (38)	250 (38)
Former	83 (24)	70 (23)	153 (24)
Current	127 (37)	118 (39)	245 (38)
Alcohol abuse, n (%):[b]			
Never	270 (78)	226 (74)	496 (76)
Former	25 (7)	29 (10)	54 (8)
Current	46 (13)	50 (16)	96 (15)
Non-cancer AIDS diagnosis, n (%)[c]	149 (43)	177 (58)	326 (50)
Nadir CD4 count, cells/μL[b]	62 (11, 174)	30 (4, 106)	45 (7, 137)
Pre-cART HIV RNA, $\log_{10}$ copies/mL[b]	5.3 (4.8, 5.7)	5.5 (4.9, 5.8)	5.4 (4.8, 5.8)
Time on cART, years	2.7 (0.5, 6.4)	3.4 (1.3, 5.6)	3.2 (0.7, 6.2)
HIV RNA suppression to $\leq$ 400 copies/mL	329 (95)	222 (73)	551 (85)
CD4 count at cancer, cells/μL[b]	238 (95, 469)	154 (23, 308)	204 (55, 393)
HIV RNA at cancer, $\log_{10}$ copies/mL[b]	2.3 (1.4, 4.4)	3.1 (1.9, 4.8)	2.6 (1.4, 4.6)

[a]Median (quartiles) unless noted otherwise.
[b]% (n) missing observations: smoking < 1% (2), alcohol < 1% (4), nadir CD4 cell count <1% (1), pre-cART HIV RNA <1% (4), CD4 cell count at cancer 7% (44), and HIV RNA at cancer 8% (51).
[c]A non-cancer AIDS diagnosis included any CDC AIDS-defining illness with the exception of NHL, KS or cervical cancer at or before cancer diagnosis.

imputed missing values 25 times using a Markov chain Monte Carlo algorithm as implemented in the SAS procedure MI [27,28]. The first 1000 Monte Carlo draws were discarded to allow for a burn-in period, and the subsequent 5000 draws were used to summarize the joint posterior density. Imputations were based on information from all variables in Tables 1 and 4, including the occurrence and timing of deaths. We estimated summary hazard ratios as the antilog of the average of the 25 log hazard ratios. We estimated the variance of the hazard ratios by Rubin's canonical imputation variance formula [27].

Results

Among a total of 20 677 HIV-infected persons enrolled in the CNICS cohort, there were 1,454 incident cases of invasive cancer. Six hundred and fifty patients treated with cART had a subsequent diagnosis of cancer between 1996 and 2009 (Table 1). The median age at cancer diagnosis was 44 years, 52% of participants were white, 86% were male, 18% reported IDU as a risk factor for transmission of HIV-infection, 21% were co-infected with viral hepatitis, 38% were current smokers (24% former), and 15% currently abused alcohol (8% former). Prior to treatment with cART, participants had a median nadir CD4 cell count of 45 cells/μL and a median HIV RNA of 5.4 $\log_{10}$ copies/mL. The initial cART regimen was anchored with an unboosted protease inhibitor (PI) in 269/650 (41%), a ritonavir boosted PI in 197/650 (30%), a non-nucleoside reverse transcriptase inhibitor (NNRTI) in 166/650 (26%), and three nucleoside reverse transcriptase inhibitors (NRTIs) in 18/650 (3%). The median time on cART before a diagnosis of cancer was 3.2 years. At the time of cancer diagnosis 92% of the patients were still on cART, which included regimens anchored with a boosted PI in 362/595 (60%) of patients, a NNRTI in 158/595 (27%), an unboosted PI in 57/595 (10%), and other medications in 18/595 (3%). At any time before cancer diagnosis, 551/650 (85%) of patients achieved HIV RNA suppression to less than or equal to 400 copies/mL. At cancer diagnosis, the median CD4 cell count was 204 cells/μLand median HIV RNA was 2.6 $\log_{10}$ copies/mL.

Infection-unrelated NADCs comprised 34% of cancers, while infection related NADCs were 17% of cancers and ADCs accounted for 49% of cancers. Overall, the most common incident cancers were KS (29%), NHL (21%), lung (9%), and anal (8%) (Table 2). Staging information was available for 256/427 (60%) of cancers that use the I-IV summary staging classification (excluding cases of KS, leukemia, multiple myeloma, primary CNS NHL, and primary brain). Of the 256 cancers classified by summary stage, 20%, 19%, 15%, and 46% were stage I, II, III, and IV, respectively. Among patients with staging information, stage IV disease was documented in 40/70 (57%) with NHL, 26/42 (62%) with lung cancer, 2/32 (6%) with anal cancer, 19/30 (63%) with Hodgkins lymphoma, 2/10 (20%) with prostate cancer, 4/12 (33%) with liver cancer, 2/9 (22%) with kidney cancer, 1/4 (25%) with breast cancer, 3/6 (50%) with colon cancer, 0/2 (0%) with melanoma, and 20/55 (36%) with other cancer types. In addition, when classifying visceral KS and primary CNS NHL as "stage IV equivalent", staging information was available for 73% of cancers (463/634, excluding 16 cases of leukemia, multiple myeloma, and primary brain cancer). The majority (237/463; 52%) of these cancers were classified as "stage IV equivalent."

Among the 650 HIV-infected patients diagnosed with invasive cancer on cART, there were 305 deaths during 1,480 person-years of follow-up for a crude mortality rate of 20.6 per 100 person-years (95% CI: 18.4, 23.1), and an overall 2-year survival of 58% (95% CI: 54, 62%) (Table 3). The highest mortality rates were among those with primary CNS NHL, liver, and lung cancer with rates per 100 person-years of 90.6, 84.3, and 68.1, respectively. The adjusted hazard ratio (HR) for death was higher among those who were older and had "stage IV equivalent" cancer (Table 4). The adjusted HR for death was lower among those who had higher CD4 cell counts at cancer diagnosis, achieved HIV RNA suppression to less than or equal to 400 copies/mL, received cancer treatment, and had ADCs or infection-related NADCs compared to infection-unrelated NADCs (Table 4 and Fig. 1). In adjusted analyses of the subset of 256 patients with known cancer summary stage, we found similar associations between all-cause mortality and age (HR = 1.26; 95% CI: 1.00, 1.60, $p = 0.05$), HIV RNA suppression (HR = 0.38; 95% CI: 0.20, 0.71, $p < 0.01$), non-cancer AIDS diagnosis (HR = 1.70; 95% CI: 1.10, 2.63, $p = 0.02$), stage IV cancer (HR = 2.88; 95% CI: 1.89, 4.37, $p < 0.01$), cancer treatment (HR = 0.41; 95% CI: 0.20, 0.84, $p = 0.02$), and infection-related NADCs (HR = 0.36; 95% CI: 0.19, 0.68, $p < 0.01$). In additional adjusted analyses of the subset of 463 patients with known "stage IV equivalent" cancer staging, we also found similar associations between all-cause mortality and age (HR = 1.47; 95% CI: 1.22, 1.77, $p < 0.01$), HIV RNA suppression (HR = 0.28; 95% CI: 0.18, 0.44, $p < 0.01$), non-cancer AIDS diagnosis (HR = 1.41; 95% CI: 1.00, 2.00, $p = 0.05$), stage IV cancer (HR = 2.68; 95% CI: 1.89, 3.80, $p < 0.01$), receiving cancer treatment (HR = 0.49; 95% CI: 0.31, 0.79, $p < 0.01$), ADCs (HR = 0.55; 95% CI: 0.35, 0.86, $p < 0.01$), and infection-related NADCs (HR = 0.43; 95% CI: 0.23, 0.78, $p < 0.01$).

Discussion

Cancer has been an important cause of morbidity and mortality for individuals with HIV-infection since the

Table 2. Characteristics of 650 incident cancer cases among HIV-infected adults treated with cART in the CNICS Cohort between 1996 and 2009.

Characteristics at cancer diagnosis:[a]	Survivors	Deaths	Overall
Total, n	345	305	650
Median year of diagnosis (Range)	6/05 (2/03; 2/07)	7/03 (5/01; 1/06)	6/04 (2/02; 9/06)
Cancer diagnosis	n (%)	n (%)	n (%)
KS	123 (36)	62 (20)	185 (29)
NHL non-CNS	43 (12)	71 (23)	114 (18)
Lung	11 (3)	48 (16)	59 (9)
Anal	40 (12)	15 (5)	55 (8)
Hodgkin	26 (7)	6 (2)	32 (5)
Prostate	21 (6)	6 (2)	27 (4)
NHL CNS	3 (1)	19 (6)	22 (3)
Liver	3 (1)	19 (6)	22 (3)
Kidney	6 (2)	13 (4)	19 (3)
Melanoma	13 (4)	2 (1)	15 (2)
Breast	8 (2)	3 (1)	11 (2)
Colorectal	7 (2)	4 (1)	11 (2)
Other [b]	41 (12)	37 (13)	78 (12)
Summary cancer diagnosis			
Infection-unrelated NADCs	99 (29)	122 (40)	221 (34)
ADCs[c]	169 (49)	152 (50)	321 (49)
Infection-related NADCs[d]	77 (22)	31 (10)	108 (17)
Summary Stage			
I	38 (11)	13 (4)	51 (8)
II	27 (8)	21 (7)	48 (7)
III	17 (5)	21 (7)	38 (6)
IV	43 (12)	76 (25)	119 (19)
Missing	86 (25)	85 (28)	171 (26)
Not Applicable[e]	134 (39)	89 (29)	223 (34)
''Stage IV equivalent'', n (%)[f]	98 (39)	139 (66)	237 (52)
Biopsy confirmation, n (%)[g]	280 (81)	262 (86)	542 (83)
Cancer treatment, n (%)[h]	270 (78)	215 (71)	485 (75)

[a]Median (quartiles) unless noted otherwise.
[b]Other cancers: cervical, biliary, bladder/urinary, primary brain, esophagus, oral cavity/pharynx, other head and neck, leukemia, multiple myeloma, other (not specified or unknown origin), ovary, pancreas, penis, peritoneum/retroperitoneum, small intestine, soft tissue, stomach, testicular, thyroid, trachea/pleura, uterus, and vagina/vulva.
[c]ADCs: cervical, Kaposi sarcoma, and Non-Hodgkin lymphoma.
[d]Infection-related NADCs: squamous cell anal, squamous cell oral cavity/pharynx, Hodgkin lymphoma, liver with viral hepatitis, vagina/vulva, and penis.
[e]Cancers that do not use I-IV summary staging: KS, primary CNS NHL, leukemia, multiple myeloma, and primary brain.
[f]Among 463 cases (251 survivors and 212 deaths) that could be classified as ''stage IV equivalent'' (excluding 171 missing and 16 cases of leukemia, multiple myeloma and primary brain). Summary stage IV, visceral KS and primary CNS NHL classified as ''stage IV equivalent.'' Summary stages I to III and mucocutaneous KS was classified as ''not stage IV equivalent;''.
[g]Biopsy confirmation obtained for 415/465 (89%) non-KS cancer diagnoses and for 127/185 (69%) of KS diagnoses.
[h]Cancer treatment information missing for 86 (13%) of patients: 39 (11%) survivors and 47 (15%) deaths.

beginning of the epidemic. Indeed, we found that in a large cohort of over 20 000 HIV-infected persons receiving care at eight major metropolitan areas across the United States, more than 3% of patients receiving antiretroviral therapy developed cancer. We identified known risk factors for mortality including older age, stage IV cancer at time of diagnosis, and lack of cancer treatment. We also found key factors associated with mortality that are specific to HIV-infected patients and have not been previously reported, including failure to suppress HIV RNA, low CD4 cell count at cancer diagnosis, and cancers unrelated to a viral co-infection. A possible explanation for these findings would be that HIV RNA reduction and immunologic recovery from cART led to suppression of viral co-infection replication and its effects on tumor pathogenesis or growth of these cancers. Alternatively, among HIV-infected patients, these cancers may be less aggressive or more responsive to cancer treatment compared with non-AIDS-defining cancers unrelated to viral co-infection. However, classifying cancers as related to viral co-infection may not be of central clinical importance when studying outcomes such as mortality. For example, in Figure 1 panel C, we observed a notable difference within infection-related NADCs in which mortality was considerably higher for those with liver cancer compared to anal cancer or Hodgkin lymphoma. These findings point to the need for further study of the epidemiology and pathophysiology of cancer progression and viral co-infections in HIV disease. In particular, more information is needed regarding outcomes of individual types of cancer among HIV-infected individuals.

We observed several important findings with regard to mortality rates for individual cancers. Consistent with reports from other HIV-infected populations, the highest

Table 3. Mortality rates and 2-year survival estimates of 650 incident cancer cases among HIV-infected adults treated with cART in the CNICS Cohort between 1996 and 2009.

	No. Persons	No. Deaths	Person Years	Mortality Rate per 100 person-years	95% Confidence Limits	2-year survival, %
Cancer diagnosis:						
NHL, primary CNS	22	19	21	90.6	58.8, 142.0	16%
Liver	22	19	23	84.3	53.8, 132.2	12%
Lung	59	48	70	68.1	51.3, 90.4	24%
NHL, non CNS	114	71	236	30.0	23.8, 37.9	47%
Kidney	19	13	54	24.2	14.0, 41.6	58%
Other[a]	78	37	160	23.2	16.8, 32.0	57%
KS, visceral	96	44	235	18.7	13.9, 25.1	64%
Colorectal	11	4	24	16.9	6.3, 45.0	NA[d]
Breast	11	3	24	12.6	4.1, 39.2	NA[d]
Anal	55	15	173	8.7	5.2, 14.4	77%
Hodgkins	32	6	95	6.3	2.8, 14.0	NA[d]
KS, mucocutaneous	89	18	241	7.5	4.7, 11.8	85%
Prostate	27	6	87	6.9	3.1, 15.3	NA[d]
Melanoma	15	2	37	5.4	1.4, 21.5	NA[d]
Summary cancer diagnosis:						
Infection-unrelated NADCs	221	122	435	28.0	23.5, 33.5	51%
ADCs[b]	321	152	734	20.7	17.7, 24.3	59%
Infection-related NADCs[c]	108	31	311	10.0	7.0, 14.2	72%
Overall	650	305	1480	20.6	18.4, 23.1	58%

[a]Other cancers: cervical, biliary, bladder/urinary, primary brain, esophagus, oral cavity/pharynx, other head and neck, leukemia, multiple myeloma, other (not specified or unknown origin), ovary, pancreas, penis, peritoneum/retroperitoneum, small intestine, soft tissue, stomach, testicular, thyroid, trachea/pleura, uterus, and vagina/vulva.
[b]ADCs: cervical, Kaposi sarcoma, and Non-Hodgkin lymphoma.
[c]Infection-related NADCs: squamous cell anal, squamous cell oral cavity/pharynx, Hodgkin lymphoma, liver with viral hepatitis, vagina/vulva, and penis.
[d]NA, not available; 2-year survival not reported for cancers with less than ten deaths.

mortality rates for non-AIDS defining cancers were among patients with liver and lung cancer [20,22], accounting for nearly 50% of deaths after non-AIDS defining cancer. Two-year survival for patients with liver cancer in this study was only 12%. Previous studies of mortality after liver cancer comparing those with and without HIV-infection have been mixed [30,31]. Mortality after NHL is known to be worse for patients with HIV, although a recent study from Europe suggested improved survival with cART [32]. Our results were consistent with another recent study of survival after NHL that directly compared those with and without HIV-infection in the cART era [33] and found 40% 2-year survival for patients with HIV and 70% for those without HIV. Our findings also suggest that HIV-infection may increase mortality for patients with kidney cancer since 2-year survival was only 58%. Considering immune-modulating therapies are often used for treatment of renal cell carcinoma, immune-deficiency or dysregulation due to HIV-infection could unfavorably alter the pathogenesis of this cancer. This finding has not been previously reported and requires further investigation.

Increased mortality observed among those with lower CD4 cell counts highlights the importance of timely HIV treatment. The majority of patients in this study had very low nadir CD4 cell counts prior to initiation of cART and were unable to adequately rebuild their immune system with treatment. This finding is consistent with several studies showing that severity of immune suppression at time of cART initiation is predictive of the ability of antiretroviral treatment to significantly increase CD4 cell count [34–37]. Ongoing inflammation and immunodeficiency in patients who initiate cART at lower CD4 cell counts increases the risk of developing co-morbid conditions as demonstrated by the prognostic value of CD4 cell count and other immunologic markers in patients treated with cART [35,38]. Our results emphasize the importance of prompt and effective treatment of HIV with cART to reduce mortality from AIDS and non-AIDS defining co-morbid conditions, such as cancer.

More than 50% of HIV-infected patients diagnosed with cancer in our cohort had advanced (stage IV) disease at the time of diagnosis. Additionally, at least 25% of patients received no cancer treatment. This is surprising, as individuals in this study were receiving cART in specialized HIV clinics and routinely engaged in care with quarterly monitoring on average. Although it is possible that HIV infection and associated immune system dysfunction accelerate the rate of cancer progression to advanced and untreatable states, our findings could be explained by poor cancer awareness, inadequate screening practices, or lack of prompt therapy. HIV-infected individuals may require novel cancer prevention and treatment strategies that incorporate

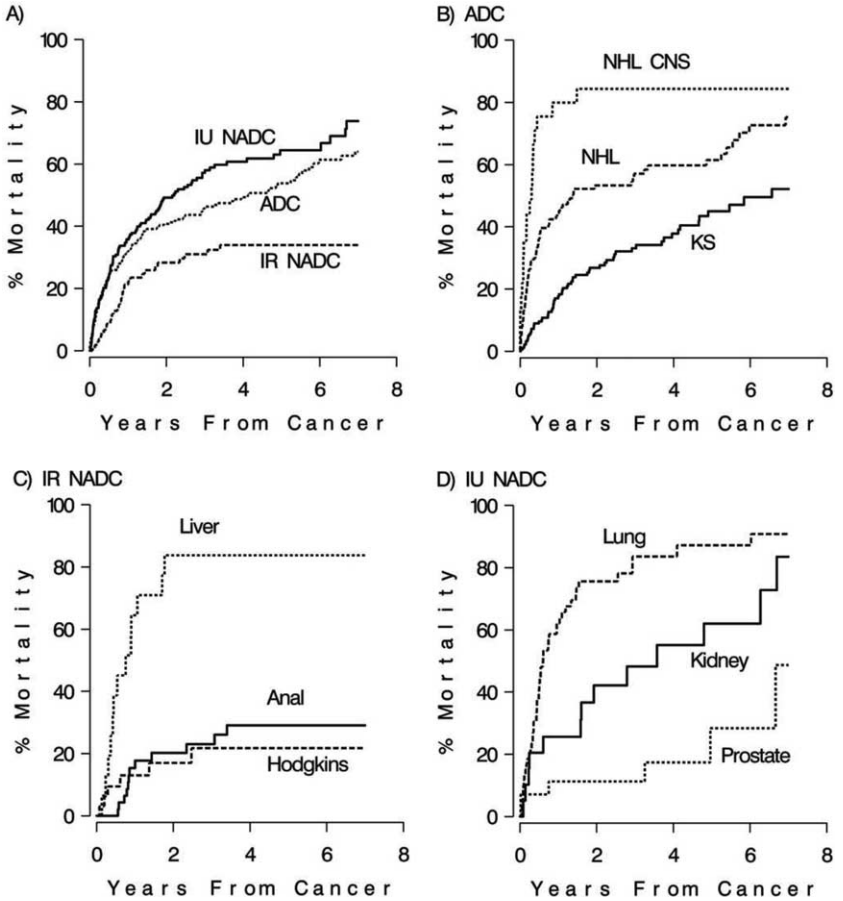

Fig. 1. Cumulative mortality over time by summary cancer type (panel A) and individual cancer types within the cancer summary categories (panels B – D). ADC, AIDS-defining cancers, IU NADC, Infection-unrelated Non-AIDS Defining cancers, and IR NADC, Infection-related Non-AIDS Defining cancers.

key prognostic factors such as those found in our study, including suppression of HIV RNA, prevention of CD4 cell count decline, and cancer screening initiated at a younger age than in the general population. Further research is needed to define the optimal timing and modalities for cancer screening and treatment among HIV-infected populations.

This study has several limitations. First, associations presented here reflect observational evidence and therefore, could have been influenced by unmeasured risk factors for death such as active substance abuse, or other co-morbid disease. Second, while the present work reflects a large study of mortality after cancer diagnosis, information regarding tobacco exposure, alcohol abuse, viral hepatitis co-infection, non-cancer AIDS diagnoses, cancer stage, and cancer treatment were subject to imprecision and potential misclassification. Third, despite extensive medical record review, detailed cancer staging information was not available for 26% of cancer diagnoses, a key predictor of mortality. However, we used multiple imputation to account for missing staging information in the final adjusted model for the full cohort, and our results were consistent with multivariable analyses conducted on two subsets of patients with known cancer stage. Fourth, we did not account for changes over time for certain factors, such as CD4 cell count and cART, which will be the focus of subsequent analyses. Lastly, we did not have information on cause of death and were unable to provide direct comparisons of our findings with a matched population of patients without HIV-infection. In the modern era of cART, patients with cancer and HIV-infection have several competing risks for death that vary depending on individual cancer type. We were limited by a small number of cases of specific cancer types and aggregate findings may not accurately capture outcomes for less common cancers. Future research in this area will require multi-center cohorts with large numbers of individuals with specific cancer types and detailed information about cause of death.

Despite these limitations, this work has several strengths. First, this was a multi-center collaborative effort from a large and diverse population with cancer diagnoses rigorously verified to minimize misclassification. Second, the occurrence and timing of mortality was based on active and passive surveillance also leading to minimal misclassification. Finally, distinct from previous studies, we were

Table 4. Adjusted mortality rate ratios of 650 incident cancer cases among HIV-infected adults treated with cART in the CNICS Cohort between 1996 and 2009.

	Adjusted Hazard Ratio[a]	95% Confidence Intervals	P value
Age, per decade	1.44	1.25, 1.66	<0.01
Non-white vs. white	1.24	0.97, 1.59	0.09
Male vs. female	1.05	0.73, 1.51	0.78
HBV/HCV infection	1.29	0.97, 1.70	0.08
Smoking:			
Current vs. never	1.00	0.76, 1.32	0.99
Past vs. never	0.77	0.56, 1.10	0.11
Alcohol abuse:			
Current vs. never	0.96	0.70, 1.32	0.81
Past vs. never	1.30	0.86, 1.95	0.22
Nadir CD4 cell count, per 100 cells/μl	0.99	0.85, 1.15	0.85
CD4 cell count at cancer, per 100 cells/μl	0.90	0.83, 0.98	0.01
HIV RNA suppression to $\leq$ 400 copies/mL	0.32	0.23, 0.44	<0.01
Pre-cART HIV RNA, per $\log_{10}$	1.00	0.86, 1.15	0.97
Non-cancer AIDS diagnosis	1.21	0.94, 1.55	0.14
''Stage IV equivalent''[b]	2.30	1.69, 3.13	<0.01
Cancer treatment	0.55	0.39, 0.79	<0.01
Date of cancer diagnosis, per year	0.99	0.95, 1.03	0.57
Summary cancer diagnosis:			
Infection-unrelated NADCs	1	Reference	
ADCs[c]	0.59	0.42, 0.81	<0.01
Infection-related NADCs[d]	0.52	0.34, 0.78	<0.01

[a]Adjusted for all variables in the Table.
[b]Summary stage IV, visceral KS and primary CNS NHL classified as ''stage IV equivalent.'' Summary stage I to III and mucocutaneous KS classified as ''not stage IV equivalent.'' In the final model, ''stage IV equivalent'' was imputed for 187/650 (29%) cases with missing information.
[c]ADCs: cervical, Kaposi sarcoma, and non-Hodgkin lymphoma.
[d]Infection-related NADCs: squamous cell anal, squamous cell oral cavity/pharynx, Hodgkin lymphoma, liver with viral hepatitis, vagina/vulva, and penis.

able to examine multiple risk factors for mortality among HIV-infected patients with cancer including CD4 cell count, HIV RNA level, cancer stage, viral hepatitis co-infection, smoking, and alcohol exposure.

In conclusion, among individuals with cancer and HIV-infection treated with cART, we observed independent effects on mortality of low CD4 cell count, lack of HIV RNA suppression and cancer treatment, and cancers unrelated to infection. In addition, a large proportion of patients engaged in routine HIV care were diagnosed late with stage IV cancer. Our results support earlier initiation of cART and aggressive cancer screening and treatment practices to maintain immunologic function, obtain optimal virologic suppression, control viral co-infections, detect cancers at an early stage, and provide appropriate cancer therapies. These findings exemplify the dynamic nature of the HIV epidemic in the current era of cART and highlight the need for continued research on prevention, diagnosis, and treatment of non-AIDS-defining conditions, including cancer.

Acknowledgements

These findings are presented on behalf of the CFAR Network of Integrated Clinical Systems (CNICS). We would like to thank all the CNICS investigators and data management teams from the eight sites who contributed to the completion of this study at Case Western Reserve University, University of Alabama at Birmingham, University of California, San Francisco, University of Washington, University of California, San Diego, Fenway Community Health Center of Harvard University, University of North Carolina, and Johns Hopkins University. We would also like to thank Drs. Ronald Mitsuyasu and Jeannette Lee for their assistance with this project. Funding for this study was provided by NIAID with a NCI supplement (R24 AI067039) and the University of Washington AIDS and STD Research Training Grant (T32 AI07140-31). In particular, we would like to acknowledge Donna Porter and Dawn Grill for their significant contributions to the CNICS.

C.J.A. worked closely with M.M.K., M.S.S., and the CNICS data management core at the University of Washington to design and implement the cancer data collection process. C.J.A. and S.R.C. designed the study and acquired the data from the CNICS data management core. S.R.C. selected the appropriate statistical analyses and executed them with the assistance of C.J.A. The initial draft of the manuscript was written by C.J.A. and S.R.C. M.M.K. and C.C. assisted in refining the statistical analysis and preparing subsequent drafts of the manuscript. Throughout the study, all authors participated in discussions about the design, statistical analyses, and interpretation of findings. All authors were involved in the review and editing process of the final manuscript for submission.

NIH Funding Sources: NIAID R24 AI067039 (with NCI supplement), NIAID T32 AI07140-31, and P30 AI 027757

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