CANCER INCIDENCE AND CANCER-ATTRIBUTABLE MORTALITY AMONG PERSONS WITH AIDS IN THE UNITED STATES: 1980-2006

by EDGAR P. SIMARD

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ABSTRACT OF THE DISSERTATION

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Context: Profound immune suppression is the hallmark of infection with the human immunodeficiency virus (HIV) and the principal sequela of chronic HIV disease is progression to acquired immunodeficiency syndrome (AIDS). There are over half a million people living with AIDS in the U.S. today and many more with HIV infection who have yet to develop AIDS. HIV-associated immune deficiency, coinfection with oncogenic viruses and elevated prevalences of smoking and alcohol use, place persons with HIV/AIDS at increased risk for a number of cancers. Highly active antiretroviral therapy (HAART), widely available since 1996, results in partial immune restoration among persons with HIV/AIDS. Concurrent with increased HAART use, declines in AIDS-related mortality and in the incidence of some cancers have been observed. However, as survival increases among persons with AIDS, little is known about their long-term cancer risk. Further, as rates of AIDS-related deaths decline, cancers may emerge increasingly important sources of mortality in this aging population.

Specific Aims: The aims of this dissertation were to: (1) determine cancer risk among persons with longstanding AIDS in years 3-5 and years 6-10 after AIDS onset, (2) to evaluate the impact of HAART on cancer incidence in years 3-10 after AIDS onset, (3) to quantify the cumulative incidence of AIDS-defining cancer and non-AIDS-defining cancer, controlling for trends in mortality, and (4) to determine the fraction of deaths among persons with AIDS attributable to cancer.

Design, Setting, and Patients: Data from the population-based U.S. HIV/AIDS Cancer Match Study (HACM) were used to address the aims of this dissertation. Records of persons with HIV/AIDS in surveillance registries from 9 states and 6 metropolitan areas (diagnosed during 1980-2008) were linked to corresponding cancer registry records using a probabilistic matching algorithm. Records were linked on demographic characteristics which were assigned a weight to represent their importance. AIDS onset date was recorded according to the 1993 Centers for Disease Control and Prevention surveillance case definition. Incident, invasive cancers were coded according to the *International Classification for Diseases for Oncology (third edition).* Subsequent to the match, all identifying information was removed. For Aims 1 and 2, we constructed a cohort of 263,254 adults and adolescents with AIDS (diagnosed during 1980-2004) and evaluated incident cancers occurring during years 3-5 and 6-10 after AIDS onset. Standardized incidence ratios (SIRs) assessed risks relative to the general population. Rate ratios (RRs) derived from Poisson regression compared cancer

incidence before and after 1996 to assess the impact of HAART. For Aims 3 and 4, we constructed a cohort of 372,364 adults and adolescents with AIDS who were alive, caner-free, and under follow-up for cancer at the start of the fourth month after AIDS onset. We used competing risk methods to determine cumulative incidence of cancer (AIDS-defining cancers [ADCs] and non-AIDS-defining cancers [NADCs]) and Cox regression to estimate cancer-attributable mortality across 3 calendar periods (AIDS onset in 1980-1989, 1990-1995, and 1996-2006).

Results: Aims 1 and 2 demonstrated risks of ADCs (Kaposi sarcoma, non-Hodgkin lymphoma, cervical cancer) were significantly elevated during 3-5 and 6-10 years after AIDS, and incidence of Kaposi sarcoma and non-Hodgkin lymphoma declined significantly between the pre-HAART (1990-1995) and HAART era (1996-2006). Other cancers with elevated risks in the 3-5 and 6-10 year periods, respectively, were cancers of the oral cavity/pharynx (SIR 1.9 95%CI 1.6-2.1, and SIR 1.8 95%CI 1.5-2.1) and anus (SIR 27 95%CI 24-31, and SIR 40 95%CI 35-45), and Hodgkin lymphoma (SIR 9.1 95%CI 7.8-11, and SIR 12 95%CI 9.7-14). Between 1990-1995 and 1996-2006, incidence increased for anal cancer (RR 2.9 95%CI 2.1-4.0) and Hodgkin lymphoma (RR 2.0 95%CI 1.3-2.9). Aims 3 and 4 demonstrated cumulative incidence of ADCs declined across AIDS calendar periods (from 8.7% among persons diagnosed with AIDS during 1980-1989 to 6.4% among persons diagnosed with AIDS during 1990-1995 to 2.1% among persons diagnosed with AIDS during 1996-2006). Cumulative

incidence of NADCs increased from 0.86% in 1980-1989 to 1.1% in 1990-1995 with little change thereafter (1.0%, 1996-2006). However, the cumulative incidence of some site-specific NADCs (anal cancer, Hodgkin lymphoma, liver cancer and lung cancer) increased. Among those with AIDS and cancer, cancer-attributable mortality increased to 88.3% (ADC) and 87.1% (NADC) during 1996-2006, and population-attributable NADC mortality increased to 2.3% (1996-2006). Population-attributable ADC mortality decreased from 6.3% (1990-1995) to 3.9% (1996-2006).

Conclusions: Among people who survived an AIDS diagnosis for several years or more, we observed continuing risks of ADCs and elevated long-term risks for selected NADCs, notably anal cancer and Hodgkin lymphoma. We also noted dramatically declining incidence of ADCs and increases in some NADCs, while controlling for temporal trends in mortality using competing risk methods. Among people with AIDS who develop cancer, their malignancy is the predominant cause of death, pointing to the need for more effective cancer treatment in this population. Further, NADCs account for a growing fraction of all deaths among persons diagnosed with AIDS in the HAART era. Continued monitoring of long-term cancer risk among persons with AIDS is warranted and should be extended to include persons with HIV infection alone. As HIV infection is increasingly considered with chronic disease management paradigms, greater attention should be focused on cancer screening and prevention strategies among person with HIV/AIDS.

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INTRODUCTION

HIV/AIDS natural history

Unexplained outbreaks of Kaposi's sarcoma and *Pneumocystis carinii* (now known as *Pneumocystis jiroveci)* pneumonia among gay men in the early 1980s were the first indications of what was later identified as human immunodeficiency virus (HIV) infection.[1,2] A member of the *Retroviridae* family, HIV is a positive-sense RNA virus which is converted to DNA through reverse transcriptase once it enters its human host.[3,4] Major cellular targets of HIV infection include the lymphoreticular, hematopoietic and nervous systems. The hallmark of chronic HIV infection is progressive depletion of $CD4^+$ T-lymphocytes (CD4).

Time from HIV infection to the development of the principal sequela of HIV infection, acquired immune deficiency syndrome (AIDS) varies, and viral, host and environmental factors are believed to play a role in progression to AIDS. Decreasing numbers of CD4 cells are associated with the rapid development of AIDS, which is characterized by the presence of profound immune suppression (<200 CD4 cells/μL or <14% of total lymphocytes in peripheral blood).[5,6]

HIV/AIDS burden of disease

The HIV/AIDS epidemic dates to the early 1980s and mathematical models demonstrate that the annual incidence of new infections peaked to a high of 130,000 in 1984 and decreased to 56,000 in 2006.[7-9] The estimated rate of

new HIV infections in the U.S. for 2006 was 22.8 per 10^5 population.[10] There are meaningful disparities in HIV infection by demographic groups, with an elevated rate among men compared to women. There are also differences by race/ethnicity: in 2006 the estimated incidence among blacks (83.7 per 10^5 population) was 7-fold higher relative to whites (11.5 per 10^5).[10] The epidemic is concentrated among groups of persons with high-risk practices such as unprotected sex (male-to-male sex or high-risk heterosexual contact) and re-used and/or shared injection drug paraphernalia.[9,11]

While the incidence of new HIV infection has declined, the prevalence of HIV/AIDS has increased as more people are living with the disease, owing to effective treatments prolonging survival. In 1996, an estimated 225,000 persons in the U.S. were living with AIDS and in 2006 prevalence increased to 509,681.[9]

HIV/AIDS is a significant cause of mortality. From the start of the epidemic through 2006, an estimated 565,927 persons have died.[9] Before antiviral therapies became available for treatment of HIV infection, survival after AIDS diagnosis was poor. Effective antiretroviral therapy became widely available in the U.S. in 1996 (referred to as highly active antiretroviral therapy or HAART) and signaled a shift in AIDS-related mortality.[13] The median 24-month survival among persons with AIDS in New York City increased from 43% in 1990-1995 to 76% in 1996-1998.[14] Among a clinic-based cohort which began recruitment in 1993, mortality decreased from 7 deaths per 100 person-years in 1996 to 1.3 deaths per 100 person-years in 2004 while the proportion of persons receiving therapy increased from 43% to 82%.[15]

Treatment

Combination therapy (HAART) utilizes medications which take synergistic action on HIV replication, and randomized controlled trials have shown HAART to be efficacious in reducing HIV viral load, increasing CD4 count and increasing overall survival.[16] The population-level effectiveness of HAART on morbidity and mortality has also been assessed by observational studies evaluating time from HIV diagnosis until AIDS onset among those who are HIV-positive and time from AIDS onset to death among those with AIDS. Both time intervals have increased in the HAART era (1996 and onwards).[14,15,17,18]

In the U.S., a substantial proportion of persons with HIV/AIDS under medical care and eligible to receive therapy are currently on HAART.[15,19] Treatment is typically indicated when the CD4 count falls below 350 cells/uL, although recent data suggest that earlier treatment may be beneficial.[20,21] Treatment access is complicated by intersecting epidemics of drug use, homelessness and marginalization which preclude many persons from routine access to care.[22] Lack of medical insurance is also a barrier to care among persons with HIV/AIDS in the U.S.[23] Adherence to HAART is important since therapy is recommended for an HIV infected patient's lifetime once indications are met. Drug toxicity and side effects further complicate adherence, and nonadherence is associated with emergence of viral drug resistance which limits effectiveness of future regimens.

Cancer and HIV/AIDS

Cancer is an important source of morbidity in the natural history of HIV/AIDS. Early in the HIV epidemic, Kaposi sarcoma (KS) was the most common cancer among HIV-positive individuals,[24] and these KS cases were recognized before the identification of HIV as the causative agent for AIDS. The link between HIV/AIDS and malignancies is similar to the increased risk for malignancies among transplant recipients on immune suppressive therapies (anti-rejection medications) which blunt immune response.[25] Immune system dysfunction plays a role in many cancers among persons with HIV/AIDS. For some cancers, the synergistic effect of HIV/AIDS-related immune suppression leading to T-cell depletion and decreased immune surveillance have been identified as important cofactors in the occurrence of malignant neoplasms.[26-28] Coinfection with oncogenic viruses and other direct and indirect carcinogenic mechanisms play a role, and have yet to be entirely understood. High-risk sexual and drug using behaviors place persons at risk not only for HIV infection but infection with other viruses known to be important in cancer etiology. Indeed, a number of viruses are considered necessary or sufficient causes of cancers observed among persons with AIDS, including human herpesvirus 8 for KS, Epstein Barr virus (EBV) for the major AIDS-defining non-Hodgkin lymphoma (NHL) subtypes (diffuse large B cell NHL and central nervous system NHL), and human papillomavirus (HPV) for cervical cancer.[29,30]

Cancers among persons with AIDS are grouped into 2 categories: AIDS-defining cancers and non-AIDS-defining cancers, based on the 1993 Centers for

Disease Control and Prevention surveillance case definition.[6] AIDS-defining cancers include KS, NHL and cervical cancer; all other cancers are considered in the non-AIDS-defining cancer group.[6]

AIDS-defining cancers

Trends in AIDS-defining cancer risk over time in the period immediately following AIDS diagnosis have been well described.[24,31,32] Declines in KS incidence began in the 1980s and continued after the widespread availability of HAART in 1996. Still, KS risk remains elevated among persons with diagnosed with AIDS recently (1996-2002) relative to the general population (e.g., standardized incidence ratio [SIR], 3640).[31] Similar dramatic declines in NHL risk have been noted and despite improvements in immune function during the HAART era, NHL continues to occur in excess among persons with AIDS.[31] Cervical cancer incidence has not changed appreciably and accounts for a small fraction of malignancies among women with AIDS (1%).

Non-AIDS-defining cancers

Early in the epidemic, AIDS-defining cancers accounted for the majority of cancers in people with AIDS. However, during the HAART era, which has been characterized by marked declines in the incidence of KS and NHL, the proportion of non-AIDS-defining cancers has increased over time, from 10.1% in 1990-1995 to 34.2% in 1996-2002.[31] While part of this shift in the profile of cancers is due simply to a decrease in AIDS-defining cancers, declines in the former explain

only part of the issue, and temporal increases in some non-AIDS-defining cancers warrant public health attention and monitoring.[24,31,32]

Lung cancer risk is elevated among persons with AIDS, at least partly due to a high prevalence of smoking,[33] and a recent analysis found lung cancer accounted for one-quarter of all non-AIDS-defining malignancies.[31] Anal cancer risk is also elevated among persons with AIDS, due to a high prevalence of infection with oncogenic HPV subtypes.[34] An excess of liver cancer also exists due to a high rate of coinfection with hepatitis B virus and/or hepatitis C virus and increased alcohol consumption.[35] Finally, as with other immune suppressed populations, persons with AIDS are at increased risk for Hodgkin lymphoma, a hematopoietic malignancy. Some evidence suggests that the relationship between Hodgkin lymphoma and immune suppression is non-linear, with highest risk manifesting at moderate levels of immune suppression.[36] Immune suppression, immune disturbance, and/or inflammation related to HIV may be involved in the etiology of other non-AIDS-defining cancers as well.[37]

Rationale

Meaningful gaps exist in the literature regarding cancer risk among persons with HIV infection. One group of special interest is persons surviving for a prolonged period after AIDS diagnosis. Long-term AIDS survivors are unique: most have been immune suppressed for many years and little is known about how prolonged immune suppression influences cancer risk. Further, people living with AIDS today are long-term survivors of AIDS, and may differ from

persons who died immediately after diagnosis. To date, evaluation of cancer risk has been limited to the first 2 years after AIDS onset, due to the inability to adjust for out-migration among persons with AIDS and lack of long-term follow-up for cancer.[24,27,31] Hence, data on long-term cancer risk are lacking.

Widespread implementation of HAART in 1996 signaled dramatic declines in AIDS-related morbidity and mortality. In one study of HIV-positive outpatients receiving HAART, the incidence of AIDS-related mortality declined during 1996-2004 from 3.8 per 1,000 persons to 0.3 per 1,000 persons, respectively; while during the same time period, there was no significant change in the rate of non-AIDS mortality.[15] As both overall mortality and HIV/AIDS-associated mortality have declined, few population-based studies have addressed whether other causes of death may be increasing. Further, as persons with AIDS live longer their cumulative incidence of sequelae, including cancer, will likely also increase. Specifically, declines in mortality will allow persons with AIDS to live long enough to develop cancer. Importantly, population-based evaluations of cancer risk controlling for these strong temporal changes in mortality, are lacking. Accurate estimates of the burden of cancer and cancer-attributable mortality are needed to inform both public health programs and clinicians treating persons with AIDS.

This dissertation endeavors to address the following public health questions: to assess the long-term cancer risk among persons with AIDS and to describe the impact of changes in cancer incidence on mortality among persons with AIDS.

The specific aims of project 1 were to:

1. Determine cancer risk among persons with longstanding AIDS in years 3-5 and years 6-10 after AIDS onset.

2. Evaluate the impact of HAART on cancer incidence in years 3-10 after AIDS onset.

The specific aims of project 2 were to:

3. Quantify the cumulative incidence of AIDS-defining cancer and non-AIDS-defining cancer, controlling for trends in mortality.

4. To determine the fraction of deaths among persons with AIDS attributable to cancer.

These aims are addressed herein in the form of the 2 manuscripts to follow.

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SPECTRUM OF CANCER RISK LATE AFTER AIDS IN THE UNITED STATES

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ABSTRACT OF MANUSCRIPT 1 OF 2

SPECTRUM OF CANCER RISK LATE AFTER AIDS IN THE UNITED STATES

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ABSTRACT

Background: Persons living with AIDS today remain at elevated cancer risk. Highly active antiretroviral therapy (HAART) has been widely available in the United States since 1996 and prolongs life, but immune function is not fully restored. As persons with AIDS live longer, accurate cancer risk estimates among these “long-term survivors” are needed.

Methods: Records of 263,254 adults and adolescents with AIDS (1980-2004) from 15 U.S. regions were matched to cancer registries to capture incident cancers during years 3-5 and 6-10 after AIDS onset. Standardized incidence ratios (SIRs) assessed risks relative to the general population. Rate ratios (RRs) compared cancer incidence before and after 1996 to assess the impact of HAART.

Results: Risks of AIDS-defining cancers (Kaposi sarcoma, non-Hodgkin lymphoma, cervical cancer) were significantly elevated during 3-5 and 6-10 years after AIDS. Incidence of Kaposi sarcoma and non-Hodgkin lymphoma declined significantly between the pre-HAART (1990-1995) and HAART era (1996-2004). Other cancers with elevated risks in the 3-5 and 6-10 year periods, respectively, were cancers of the oral cavity/pharynx (SIR 1.9 95%CI 1.6-2.1, and SIR 1.8

95%CI 1.5-2.1) and anus (SIR 27 95%CI 24-31, and SIR 40 95%CI 35-45), and Hodgkin lymphoma (SIR 9.1 95%CI 7.8-11, and SIR 12 95%CI 9.7-14). Between 1990-1995 and 1996-2006, incidence increased for anal cancer (RR 2.9 95%CI 2.1-4.0) and Hodgkin lymphoma (RR 2.0 95%CI 1.3-2.9).

Conclusions: Among people who survived an AIDS diagnosis for several years or more, we observed continuing risks of AIDS-defining cancers and elevated long-term risks for selected non-AIDS-defining cancers, notably anal cancer and Hodgkin lymphoma.

SPECTRUM OF CANCER RISK LATE AFTER AIDS IN THE UNITED STATES

Introduction

Persons infected with human immunodeficiency virus (HIV) have an increased risk of cancer. [1;2] Advanced HIV infection is characterized by profound immunosuppression (i.e., acquired immunodeficiency syndrome [AIDS]), a risk factor for a number of malignancies. Three cancers are AIDS-defining: Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), and cervical cancer.[3] These cancers are themselves caused by oncogenic viruses, specifically, Kaposi's sarcoma-associated herpesvirus for KS, Epstein Barr virus for the major AIDS-defining NHL subtypes (diffuse large B cell NHL and central nervous system [CNS] NHL), and human papillomavirus (HPV) for cervical cancer.[4;5] In addition, persons with AIDS have a higher prevalence of lifestyle-related risk factors for cancer including an excess of smoking and alcohol abuse.[6;7]

Use of highly active antiretroviral therapy (HAART) among persons with HIV/AIDS can lead to partial restoration of immunity and prolonged survival.[8;9] Despite declines in cancer incidence attributable to the introduction of HAART in 1996, cancer risk among HIV-infected people remains elevated during the HAART era,[2;10-12] As persons with AIDS continue to live longer, the number of people surviving for years after an AIDS diagnosis will increase. This growing population comprises individuals who have experienced and may continue to live for a prolonged period with moderate or advanced immune deficiency. The effects of these chronic immune disturbances, HAART, and long-term infection

with oncogenic viruses are unknown. Of note, prior studies of cancer risk in HIV-infected people have been limited to follow-up during the first 1-5 years after AIDS onset,[1;2;12-14] or have not specified the period of observation after AIDS.[15-17] Accurate estimates of cancer risk are needed to inform both public health officials and clinicians treating persons with longstanding AIDS.

To assess the long-term cancer risk among persons who have survived AIDS for a number of years, we analyzed data from the HIV/AIDS Cancer Match Study, a large and representative cohort of persons with AIDS in the U.S. We evaluated the period 3-10 years after AIDS onset and sought to describe cancer risk relative to the general population and the impact of HAART on cancer incidence over time.

Methods

Study Design

The HIV/AIDS Cancer Match Study links records of persons with HIV or AIDS diagnosed between 1980 and 2008 from 15 U.S. states and metropolitan regions to corresponding cancer registry records using a probabilistic algorithm.[1] Cancer registry coverage varies by region but is complete through 2004-2006 for several registries. Following linkage of registry databases, only de-identified data were retained for analyses. Institutional review boards at participating sites approved the study.

The current study focuses on cancer risk late after an AIDS diagnosis, specifically for the period 3-10 years after AIDS onset. AIDS onset was defined

using the 1993 Centers for Disease Control and Prevention definition.[3] The study was restricted to the most common racial/ethnic categories (non-Hispanic whites, non-Hispanic blacks, and Hispanics) to allow for stable estimates of expected cancer counts. Children less than 15 years of age were excluded. The current study was therefore limited to adults and adolescents who had AIDS onset in 1980-2004 and whose observation during the 3-10 year period after AIDS onset overlapped with cancer registry coverage (N=263,254).

Malignancies reported to cancer registries were coded according to the *International Classification for Diseases for Oncology* (third edition).[18] Cancers were categorized by site and histology using the Surveillance, Epidemiology, and End Results (SEER) program's "site recode with Kaposi sarcoma and mesothelioma".[19] This classification was slightly modified by grouping some rare cancer types and expanding others (e.g., NHL) into subtypes of special interest. Both first and subsequent malignancies of different types were considered.

Statistical Analysis

We initially evaluated cancer risk separately for the periods 3-5 and 6-10 years after AIDS onset. For each period, cancer cases and person-time were tabulated from the start of the period or the beginning of cancer registry coverage (whichever occurred later) until the earliest of the end of the period, end of cancer registry coverage, or death (as ascertained from HIV/AIDS registries). For each cancer, we present the standardized incidence ratio (SIR), defined as the ratio of observed to expected number of cancer cases, as a measure of risk

relative to the general population. Expected counts were obtained by applying gender, age, race/ethnicity, calendar year, and registry-specific incidence rates to person-time among people with AIDS. Because virtually all KS and CNS NHL cases in the general population are AIDS-related, we used expected counts for these cancers obtained from SEER registries prior to the epidemic (1973-1979).[20] We calculated two-sided exact Poisson 95% confidence intervals (CIs) for the SIRs.

Similarly, for the combined period 3-10 years after AIDS onset, we evaluated cancer risk for two attained calendar periods: 1990-1995 (pre-HAART era) and 1996-2006 (HAART era). These "attained" calendar periods correspond to those current years regardless of how long an individual had had AIDS, providing that the onset of AIDS was within 3-10 years previously. In these analyses, we calculated incidence rates as the observed counts divided by person-time at risk. Changes in incidence between the pre-HAART and HAART eras were then assessed using a rate ratio (RR) obtained from Poisson regression. The Poisson models were adjusted for attained age (age at cancer diagnosis), race/ethnicity, and gender/mode of HIV exposure (men who reported male-to-male sex [MSM] alone or with injection drug use [IDU], all other men, and females). To account for under- or over-dispersion in the Poisson models, the standard errors of the coefficients were adjusted by Pearson's chi-square statistic divided by the degrees of freedom. When a RR was zero or undefined due to an empty cell, we calculated a one-sided exact 95% CI. Using data

restricted to the HAART era, we also present SIRs for the combined 3-10 year period, as a measure of cancer risk relative to the general population.

For selected cancers with substantial changes in incidence and sufficient sample size, we calculated incidence as a function of individual attained calendar years. This analysis was restricted to years 1990-2006 in order to describe trends in the most recent calendar period, and to utilize the most observations. We used joinpoint regression to fit log-linear Poisson models for these year-specific rates, which translated into annual percentage changes across calendar time.[21] All joinpoint models were evaluated for adequate fit using the Hosmer-Lemeshow statistic. In the figures illustrating these fitted trends, we present only annual percentage changes which were significantly different from zero. We used the Joinpoint Regression Program (National Cancer Institute, Rockville, Maryland) for joinpoint anaylses and SAS, version 9.1 (SAS Institute, Cary, North Carolina) for all other statistical analyses. *P*-values <0.05 were considered significant.

A consideration in evaluating cancer risk late after an AIDS onset is that people with AIDS, after an extended period, may have migrated out of the cancer registry region. Persons with AIDS in our study were known to reside in the cancer registry coverage area at the time of AIDS diagnosis, but we had no data on subsequent out-migration. Prior studies have demonstrated that among persons with AIDS who had died, as many as 10% had moved from their area of AIDS diagnosis before death.[22;23] Similar migration rates have been noted among the general population.[24] If a person had moved out of the cancer

registry coverage area, his or her cancer would not have been ascertained, leading to a reduction in the observed cancer count but not in the estimated follow-up time, and thus causing an under-estimation of cancer risk. To correct this bias, we adjusted for potential out-migration by incrementally discounting each subject's person-time to reach a total reduction of 10% by 10 years after AIDS diagnosis. All SIR and incidence measures utilized these adjusted person-time estimates. Results were similar in a sensitivity analysis in which we discounted the person-time by a factor of 20% (APPENDIX II).

Results

Demographic characteristics of the 263,254 persons with AIDS included in the study are presented in Table 1. Most were male (80.1%), and the median age at AIDS onset was 36 years. Similar proportions of subjects were non-Hispanic white (39.7%) and non-Hispanic black (40.1%), and 20.2% were Hispanic. Almost half (44.8%) reported MSM and 24.8% had IDU as their mode of HIV exposure. These characteristics did not differ between subjects who contributed observation time to the 3-5 year period and subjects who contributed to the 6-10 year period after AIDS onset (Table 1). CD4 counts at AIDS onset were higher for subjects who contributed follow-up to the 6-10 year period than for those who contributed follow-up only to the 3-5 year period (median 144 vs. 132 cells/μL), consistent with better immune status at AIDS onset conveying longer survival. Additionally, few persons diagnosed with AIDS in 1980-1989 survived long enough to provide follow-up in the 6-10 year period. Also, some

people diagnosed with AIDS in 1996-2004 did not have enough time to be followed into the 6-10 year period. As a result, most observation time in the 6-10 year period was provided by people diagnosed with AIDS in 1990-1995 (Table 1).

Risks for the three AIDS-defining cancers were significantly elevated in years 3-5 and 6-10 after AIDS onset (Table 2). KS risk was extremely high in both time periods (SIRs 5321 and 1347 respectively), and risk of NHL was also elevated in both periods (SIRs 32 and 15, respectively). Likewise, risks were substantially higher than in the general population for the AIDS-defining NHL subtypes, namely diffuse large B-cell NHL, Burkitt NHL, and especially CNS NHL (Table 2). Cervical cancer risk was increased after AIDS during years 3-5 (SIR 5.6) and years 6-10 (SIR 3.6).

Among non-AIDS-defining cancers (Table 2), risks were elevated in both the 3-5 and 6-10 year periods for cancers of the oral cavity/pharynx, tongue, anus, liver, larynx, lung/bronchus, and penis, and for Hodgkin lymphoma. Compared to the general population, risks for anal cancer were especially high (SIRs 27 in the 3-5 year period, 40 in the 6-10 year period). Among Hodgkin lymphoma subtypes, risk was most elevated for the mixed cellularity subtype (SIRs 15 in the 3-5 year period, 17 in the 6-10 year period). Other malignancies for which risk was increased in only one of the two periods after AIDS onset included cancers of the lip and vagina/vulva, and myeloma, lymphocytic leukemia, and myeloid/monocytic leukemia (Table 2). In both time periods, risk was lower than in the general population for cancers of the breast and prostate,

and during years 3-5 after AIDS for kidney cancer. Overall, for all non-AIDS cancers combined, risk was significantly elevated after AIDS in both years 3-5 (SIR 1.7) and years 6-10 (SIR 1.6).

Table 3 compares cancer incidence in the 3-10 years after AIDS for the pre-HAART era (1990-1995) and HAART era (1996-2006). KS incidence declined by 80% (RR 0.2 95%CI 0.2-0.2) between the pre-HAART and HAART eras. A joinpoint model fitted to the incidence data revealed that this change corresponded to a steep decline during 1994-1997 (44.3% per year, Figure 1A). Similarly, NHL incidence was 70% lower in the HAART era (RR 0.3 95%CI 0.2-0.3) than in the pre-HAART era, and the joinpoint model indicated that this corresponded to a 36.9% annual reduction during 1995-1998 (Figure 1B). Declines were similar in magnitude for diffuse large B-cell NHL and CNS NHL (Table 3, Figures 1C and 1D). In contrast, the change in Burkitt NHL incidence was weaker (RR 0.6 95%CI 0.4-1.0), and cervical cancer incidence did not change significantly (RR 0.8 95%CI 0. 5-1.2). During the HAART era, persons with AIDS continued to have significantly higher risk for all AIDS-defining cancers than people in the general population (SIRs, Table 3).

Among the non-AIDS-defining malignancies, anal cancer and Hodgkin lymphoma exhibited three-fold and two-fold increases between the pre-HAART and HAART eras (RRs 2.9 and 2.0, respectively; Table 3). For anal cancer, the joinpoint model demonstrated a 10.7% annual increase in incidence over the entire 1990-2006 period, despite a small decline in the observed rate during most recent years (Figure 2A). For Hodgkin lymphoma overall, the joinpoint model

showed a 14.1% annual increase during 1990-2000, with no significant change subsequently (Figure 2B). The increase in Hodgkin lymphoma incidence was most apparent for the mixed cellularity subtype (Table 3). During the HAART era, risks of anal cancer (SIR 32) and Hodgkin lymphoma (SIR 11) remained significantly elevated relative to the general population (Table 3). Incidence of lung cancer, the most common non-AIDS-defining cancer, was marginally lower in the HAART era than in the pre-HAART era (RR 0.8 95%CI 0.6-0.9; Table 3). However, this decline over time was not manifest in the joinpoint model (Figure 2C). There were increases in the HAART era for other less common non-AIDS-defining cancers including cancers of the tongue (RR 2.9) and prostate (RR 1.6).

Overall, the incidence of all non-AIDS cancers increased 20% between the pre-HAART and HAART eras (RR 1.2 95%CI 1.0-1.3; *P*=0.006). This increase corresponded to a 4.3% annual increase during 1990-2006, although there was a suggestion that incidence declined in the most recent few years (Figure 2D). During the HAART era, people with AIDS had a 60% higher risk for non-AIDS cancers than did people in the general population (SIR 1.6 95%CI 1.6-1.7).

Discussion

This study represents one of the longest and most complete follow-up of persons with AIDS with respect to cancer risk. Our population-based data demonstrated that people with AIDS in the U.S. continue to be at elevated risk for a spectrum of AIDS-defining and non-AIDS-defining cancers years after AIDS

diagnosis. While the incidence of KS and NHL has declined substantially in the HAART era, the overall incidence of non-AIDS-defining cancers has risen. Two malignancies in particular, anal cancer and Hodgkin lymphoma, have increased in incidence in recent calendar years.

Among HIV-infected individuals, HAART use has been associated with major decreases in KS and NHL risk, and these decreases have translated into declines in incidence measurable at the population level.[2;12;25;26] We demonstrated that while persons with AIDS remain at considerable risk for KS, incidence of this malignancy first started to decline in 1995, possibly due to use of early combination antiretroviral therapy (e.g., dual nucleoside therapy), and continued to decline dramatically from 1996 onwards. Likewise, declines in the incidence of diffuse large B-cell NHL and CNS NHL coincided with introduction of HAART in 1996. HIV-induced immunosuppression, indicated by low CD4 count, is directly related to risk of KS and these NHL subtypes, and declining incidence in people with longstanding AIDS is plausibly linked to the effectiveness of HAART in improving immune function.[27] In contrast, we noted a less dramatic decline in the incidence of Burkitt NHL, a subtype whose incidence is not closely associated with CD4 count. Despite overall declines in NHL incidence, NHL was the most common malignancy in this population during the HAART era. The ongoing occurrence of KS and NHL highlights continued difficulties in providing uniform access to care and, to some extent, the incomplete effectiveness of antiretroviral therapies in people with advanced AIDS due to the presence of drug-resistant virus or limited immune reconstitution.[28-30]

Notable excess risks were observed for cancers of anus, penis, cervix, vagina and vulva, and certain sites in the head and neck (oral cavity, pharynx, tongue), all of which can be attributed to persistent infection with oncogenic HPV subtypes.[5;31] Anal cancer risk was strongly elevated up to 10 years after AIDS onset and, consistent with other reports,[10;32;33] we found that anal cancer incidence increased in the HAART era. This rise was likely not due only to increased anal cancer screening, which has been recommended for HIV-infected MSM,[34] because the increasing trend was observed for both men and women, and for regionally advanced disease (which would be detected without screening) as well as for localized disease (data not shown). The continued rise of anal cancer incidence in recent years, even in the presence of widespread HAART use, suggests instead that the key steps susceptible to immune control might have occurred years earlier, and that prolonged survival among people with AIDS has now allowed for the manifestation of invasive cancer. A similar explanation related to the long latency of the carcinogenic effects of HPV may explain why cervical cancer incidence in women has not declined in the HAART era. HIV-infected women should be screened annually for cervical cancer.[35] A prophylactic HPV vaccine is now available to prevent cervical infection, however its impact will not be realized for several decades, and its efficacy in preventing infection in HIV-positive women or in preventing anal infection is unknown.[36]

Hodgkin lymphoma risk was also substantially elevated among people with AIDS, and we noted a two-fold increase in Hodgkin lymphoma incidence in this population between the pre-HAART and HAART eras. Our joinpoint model

demonstrated that this increase was largely due to a significant rise throughout 1990-2000. Mixed cellularity Hodgkin lymphoma was the most common subtype and in the context of AIDS, is often associated Epstein Barr virus infection.[1;37] Interestingly, Biggar, et al, reported that AIDS-related immunosuppression appears to have a non-linear effect on Hodgkin lymphoma risk. Specifically, Hodgkin lymphoma risk increases as the CD4 count declines, reaches a peak when the CD4 count is approximately 225 to 249 cells/μL, and then falls again at very low CD4 counts.[37] A subsequent study did not confirm this non-linear relationship.[38] Nonetheless, among people with advanced AIDS, it is possible that use of increasingly effective HIV therapies during the HAART era has resulted in a shift in immune function associated with higher Hodgkin lymphoma risk.

Importantly, we observed a 20% overall increase in the incidence of non-AIDS-defining cancers in this population. Because cancer risk was calculated as a rate (i.e., number of events per unit of follow-up time), this rise in incidence cannot be explained simply by a decline in AIDS-related mortality and a consequent increase in time at risk for cancer. Also, the median attained age increased from 33 to 44 years over the 24-year calendar period of the study, reflecting aging of the U.S. AIDS population with improved survival. Nonetheless, our multivariable analyses comparing cancer risk in different calendar periods adjusted for attained age. Thus, the rate ratios that we report correspond to changes in cancer risk that cannot be explained by aging within the cohort. Instead, we believe that the recent overall increase in incidence of

non-AIDS-defining cancers is largely driven by the rises in anal cancer and Hodgkin lymphoma incidence noted above. Indeed, when those malignancies were excluded, the change in incidence of all non-AIDS-defining cancers between the pre-HAART and HAART era was no longer apparent (RR 1.0, 95%CI 0.9-1.1).

Other specific non-AIDS-defining cancers deserve brief comment. Lung cancer was the most frequent non-AIDS-defining malignancy, accounting for 41% of all non-AIDS cancers, although the incidence did not change meaningfully over time. Among HIV-infected individuals, the high risk of lung cancer is partly explained by tobacco use, but HIV may amplify the carcinogenic effects of smoking.[39] Liver cancer risk was elevated among people with longstanding AIDS, reflecting the carcinogenic effects of hepatitis B and C viruses, and alcohol use.[40] Finally, people with longstanding AIDS had a lower risk of prostate and breast cancers than the general population, as has been noted in other studies,[14;41] and we found that prostate cancer incidence increased between 1990-1995 and 1996-2006. These patterns could result from hormonal factors or other differences in HIV-infected individuals, which may have changed over time, or could partly reflect low rates of screening compared with the general population.[41]

Strengths of our study include its large size and population-based nature, representing all major U.S. regions and demographic groups affected by the AIDS epidemic. Other strengths include the long period of evaluation of cancer risk up to 10 years after AIDS onset, and our correction during this time for the

effects of out-migration on measured cancer risk. A limitation of our study is that we lacked individual-level data on important cancer risk factors such as smoking, illicit drug use, and HAART use.

It should be noted that ascertainment of HIV transmission category and CD4 count during 1990-1995 was incomplete, and surveillance practices changed in 1993, when the AIDS case definition was expanded to include persons with CD4 counts <200 cells/uL.[3] As such, interpreting trends in these characteristics requires statistical adjustments which we were unable to conduct. For HIV transmission category, adjustments are made at the national level which redistribute persons with unknown/missing risk factors to other categories, using multiple imputation methods.[42] While the data presented in Table 1 are unadjusted, the trends in HIV transmission category by calendar period of AIDS onset are consistent with national adjusted estimates.[42] With regards to CD4 data, ascertainment and reporting of CD4 counts was not systematic or consistently done in the early to mid 1990s; therefore, any trend in CD4 count data should be interpreted with caution.

The change in the 1993 AIDS case definition resulted in an increase in cases reported during the months immediately following implementation; most of which were reported because they met the new immunologic criteria for AIDS (CD4 count <200 cells/uL).[43] It is difficult to determine the impact of this influx of AIDS cases on our findings regarding cancer risk. However, we hypothesize that any potential impact would be to risks of AIDS-defining cancers associated with immune suppression (i.e.: KS and NHL). It is reasonable to suggest that persons

with a CD4 counts <200 cells/uL, but not much lower, would have lower risk of KS and NHL, because risk of these cancers increases with worsening immune suppression. The analyses of cancer incidence by current calendar year would be most impacted by this change. We evaluated cancer incidence during the 3-10 years after AIDS onset. As such, cancers among persons diagnosed with AIDS during 1993 occurred during current calendar years 1995 and onwards and cancers occurring among persons diagnosed with AIDS during 1994 occurred during current calendar year 1996 and onwards. We may have potentially over-estimated the impact of HAART on the incidence of KS and NHL, as the incidence in current calendar years 1996 and onwards would be arbitrarily reduced due to the bolus of persons with CD4 counts <200 cells/uL included in those years and their lower risk for immune deficiency associated-cancers. Following the same reasoning, the annual percentage changes presented from the joinpoint regression analyses of cancer incidence by current calendar year may have also over estimated the decline in incidence for these two cancer types relative to widespread HAART use in 1996. However, because the current analyses was focused on years 3-10 after AIDS, it is unlikely that the circumstances under which a person met the AIDS case definition 2-8 years prior would have a major impact on their subsequent cancer risk, as persons with AIDS initiate HAART and immune status changes. Nonetheless, our results accurately reflect the aggregate impact of these factors, and changes in their prevalence over time, on cancer incidence at the population level. Changing AIDS surveillance practices and modifications to the AIDS case definition make

adjustments to our data complicated, and any such adjustments are beyond our expertise and the scope of this project.

In summary, individuals with AIDS remain at substantially increased risk for cancer for up to 10 years after AIDS onset. Declines in KS and NHL incidence in recent years can be attributed to introduction and wide availability of HAART, but rates of these cancers continue to be elevated in people with AIDS. Further reductions may be realized with improvements in access to HAART, more effective regimens targeting drug-resistant HIV strains, and perhaps interventions to boost immune restoration even with HAART use. Of concern, we also observed an increasing incidence of anal cancer and Hodgkin lymphoma. As persons with AIDS continue to live longer after an AIDS diagnosis and as they age, it is possible that cancer risk will increase further. Future long-term evaluations of cancer risk will therefore become more important in this population.

Table 1. Demographic characteristics of persons with AIDS in the United States, 1980-2004 (N=263,254)

Characteristic	Subjects contributing follow-up time for specified periods after AIDS onset: Overall: Years 3-10 after AIDS		Years 3-5 after AIDS		Years 6-10 after AIDS	
Total No.	263,254		261,282		135,163	
Sex, n (%)						
Male	210,841	(80.1)	209,119	(80.0)	109,133	(80.7)
Female	52,413	(19.9)	52,163	(20.0)	26,030	(19.3)
Age in years at AIDS onset, n (%)						
15-29	46,059	(17.5)	45,425	(17.4)	25,656	(19.0)
30-39	121,845	(46.3)	120,963	(46.3)	63,890	(47.3)
40-49	71,074	(27.0)	70,739	(27.1)	34,924	(25.8)
50+	24,276	(9.2)	24,155	(9.2)	10,693	(7.9)
Median	36		36		36	
Race/ethnicity, n (%)						
Non-Hispanic white	104,402	(39.7)	103,406	(39.6)	55,790	(41.3)
Non-Hispanic black	105,761	(40.1)	104,957	(40.2)	52,354	(38.7)
Hispanic	53,091	(20.2)	52,919	(20.2)	27,019	(20.0)
Mode of HIV exposure, n (%)						
MSM	118,042	(44.8)	116,957	(44.8)	62,696	(46.4)
IDU	65,157	(24.8)	64,777	(24.8)	33,778	(25.0)
MSM and IDU	16,341	(6.2)	16,120	(6.2)	9,037	(6.7)
Heterosexual	11,650	(4.4)	11,582	(4.4)	6,118	(4.5)
Other/unknown	52,064	(19.8)	51,846	(19.8)	23,534	(17.4)
CD4 count at AIDS onset (cells/μL), n (%)						
0-99	74,656	(28.4)	75,845	(29.0)	35,121	(26.0)
100-199	81,885	(31.1)	81,603	(31.2)	45,409	(33.6)
200+	33,045	(12.6)	32,989	(12.6)	19,609	(14.5)
Missing	73,668	(27.9)	70,845	(27.2)	35,024	(25.9)
Median	132		132		144	
Calendar year at AIDS onset, n (%)						
1980-1989	28,318	(10.8)	26,868	(10.3)	12,025	(8.9)
1990-1995	128,296	(48.7)	127,774	(48.9)	83,564	(61.8)
1996-2004	106,640	(40.5)	106,640	(40.8)	39,574	(29.3)

Table 1 notes
In the 3-10, 3-5 and 6-10 years columns, subjects are included if they contributed person-time at-risk for cancer during those periods after AIDS onset, respectively.
Abbreviations: MSM, male-to-male sex; IDU, injection drug use.

Table 2. Cancer risk in people with AIDS for the period 3-10 years after AIDS onset

	Years 3-5 after AIDS			Years 6-10 after AIDS		
Cancer type	**No. cases**	**SIR**	**95%CI**	**No. cases**	**SIR**	**95%CI**
All cancer	9053	**6.1**	**(6.0-6.3)**	3476	**3.0**	**(2.9-3.1)**
AIDS-defining cancers						
Kaposi sarcoma	3136	**5321**	**(5137-5511)**	615	**1347**	**(1243-1458)**
Non-Hodgkin lymphoma	3345	**32**	**(31-33)**	1048	**15**	**(14-16)**
Diffuse large B-cell NHL	1618	**44**	**(42-46)**	555	**23**	**(21-25)**
Burkitt NHL	95	**29**	**(23-35)**	52	**23**	**(17-30)**
CNS NHL	989	**2005**	**(1882-2134)**	182	**474**	**(408-548)**
Other/unspecified NHL	1632	**25**	**(24-27)**	441	**10**	**(9-11)**
Cervix	101	**5.6**	**(4.5-6.8)**	38	**3.6**	**(2.6-5.0)**
Non-AIDS-defining cancers						
Oral cavity/pharynx	199	**1.9**	**(1.6-2.1)**	149	**1.8**	**(1.5-2.1)**
Lip	14	**5.4**	**(2.9-9.0)**	5	2.6	(0.8-6.0)
Tongue	27	**1.8**	**(1.2-2.5)**	34	**2.7**	**(1.9-3.8)**
Esophagus	29	1.4	(0.9-1.9)	25	1.5	(1.0-2.2)
Stomach	35	1.2	(0.8-1.7)	23	1.0	(0.7-1.5)
Small intestine	5	0.8	(0.3-1.8)	1	0.2	(0-1.1)
Colon/rectum	129	1.0	(0.8-1.2)	98	0.9	(0.7-1.1)
Anus	219	**27**	**(24-31)**	267	**40**	**(35-45)**
Liver	86	**3.7**	**(3.0-4.6)**	95	**4.5**	**(3.7-5.5)**
Pancreas	22	0.8	(0.5-1.3)	25	1.1	(0.7-1.7)
Larynx	67	**2.7**	**(2.1-3.4)**	61	**3.1**	**(2.4-4.0)**
Lung/bronchus	531	**3.0**	**(2.8-3.3)**	357	**2.6**	**(2.3-2.9)**
Bones/joints	5	1.3	(0.4-3.0)	0	0	(0-1.4)
Soft tissue	23	1.6	(1.0-2.5)	14	1.4	(0.8-2.4)
Melanoma of the skin	58	1.2	(0.9-1.5)	38	1.0	(0.7-1.3)
Breast	68	**0.6**	**(0.5-0.8)**	36	**0.5**	**(0.3-0.7)**
Uterus	7	0.6	(0.2-1.1)	4	0.4	(0.1-1.1)
Ovary	14	1.5	(0.8-2.6)	3	0.5	(0.1-1.5)
Vagina/vulva	13	1.7	(0.0-9.3)	10	**6.7**	**(3.2-12.3)**

Prostate	130	**0.5**	**(0.4-0.6)**	111	**0.5**	**(0.4-0.6)**
Testis	26	0.9	(0.6-1.2)	14	0.8	(0.4-1.3)
Penis	7	**3.2**	**(1.3-6.6)**	14	**8.5**	**(4.6-14.2)**
Bladder	28	0.9	(0.6-1.4)	20	0.8	(0.5-1.3)
Kidney	30	**0.6**	**(0.4-0.9)**	31	0.8	(0.5-1.1)
Brain	16	0.6	(0.4-1.0)	13	0.7	(0.4-1.2)
Thyroid	20	0.7	(0.5-1.10	12	0.6	(0.3-1.0)
Hodgkin lymphoma	184	**9.1**	**(7.8-11)**	145	**12**	**(9.7-14)**
Nodular sclerosis HL	50	**4.9**	**(3.7-6.5)**	38	**6.2**	**(4.4-8.5)**
Mixed cellularity HL	61	**15**	**(11-19)**	41	**17**	**(12-23)**
Other HL	73	**12**	**(9.4-15)**	66	**16**	**(13-21)**
Myeloma	31	**1.6**	**(1.1-2.2)**	10	0.6	(0.3-1.2)
Lymphocytic leukemia	15	**2.7**	**(1.5-4.5)**	2	0.5	(0.1-1.9)
Myeloid/monocytic leukemia	49	**2.5**	**(1.9-3.4)**	13	1.0	(0.5-1.6)
Mesothelioma	2	0.8	(0.1-2.9)	2	1.0	(0.1-3.7)
Miscellaneous	186	**2.8**	**(2.4-3.3)**	220	**2.5**	**(2.2-2.8)**
Poorly specified	316	**7.3**	**(6.5-8.7)**	119	**3.7**	**(3.1-4.4)**
All non-AIDS cancers	2155	**1.7**	**(1.6-1.8)**	1656	**1.6**	**(1.6-1.7)**

Table 2 notes
The miscellaneous category includes other cancers with specified topography and histology. The poorly specified category includes cancers of any topography with a poorly specified histology (ICD-O histology codes 8000-8005). The all non-AIDS cancers category excludes AIDS-defining and poorly specified cancers. Bolded values are significant at $P<0.05$. Abbreviations: CI, confidence interval; CNS, central nervous system; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; SIR, standardized incidence ratio.

Table 3. Changes in cancer risk in the HAART era (1996-2006)

Cancer type	Incidence, per 10^5 person-years: Pre-HAART era	HAART era	RR	95%CI	SIR in the HAART era	95%CI
All cancer	2968	989	**0.3**	**(0.3-0.4)**	**3.1**	**(3.0-3.2)**
AIDS-defining cancers						
Kaposi sarcoma	1282	190	**0.2**	**(0.2-0.2)**	**1584**	**(1486-1687)**
Non-Hodgkin lymphoma	1226	306	**0.3**	**(0.2-0.3)**	**15**	**(14-16)**
Burkitt NHL	22	14	**0.6**	**(0.4-1.0)**	**26**	**(20-32)**
Diffuse large B-cell NHL	590	156	**0.3**	**(0.3-0.3)**	**22**	**(20-23)**
CNS NHL	414	63	**0.2**	**(0.1-0.2)**	**592**	**(527-662)**
Other NHL	614	136	**0.2**	**(0.2-0.3)**	**11**	**(9.8-12)**
Cervix	16	16	0.8	(0.5-1.2)	**5**	**(4.0-6.2)**
Non-AIDS-defining cancers						
Oral cavity/pharynx	35	40	1.0	(0.7-1.4)	**1.8**	**(1.5-2.0)**
Lip	4	2	0.6	(0.2-2.0)	**3.6**	**(1.7-6.8)**
Tongue	2	8	**2.9**	**(1.1-7.7)**	**2.3**	**(1.6-3.2)**
Esophagus	5	6	0.9	(0.4-2.0)	1.4	(0.9-2.0)
Stomach	5	7	1.0	(0.5-2.4)	1.2	(0.8-1.7)
Small intestine	1	1	1.0	(0.1-11)	0.4	(0.1-1.2)
Colon/rectum	24	26	1.0	(0.7-1.4)	0.9	(0.8-1.1)
Anus	22	62	**2.9**	**(2.1-4.0)**	**32**	**(29-36)**
Liver	10	23	1.9	(0.9-3.9)	**4.4**	**(3.6-5.2)**
Pancreas	2	6	2.2	(0.4-13)	1.0	(0.7-1.4)
Larynx	9	15	1.3	(0.8-2.3)	**3.0**	**(2.3-3.7)**
Lung/bronchus	98	100	**0.8**	**(0.6-0.9)**	**2.6**	**(2.4-2.8)**
Bones/joints	0	1	∞	(0.2-∞)	1.1	(0.3-2.8)
Soft tissue	4	4	0.9	(0.3-2.4)	1.4	(0.9-2.2)
Melanoma of the skin	10	10	1.1	(0.5-2.3)	1.1	(0.8-1.4)
Breast	5	13	1.8	(1.0-3.2)	**0.7**	**(0.5-0.8)**
Uterus	1	1	1.4	(0.3-7.4)	0.5	(0.2-1.0)
Ovary	2	2	0.5	(0.2-1.6)	1.0	(0.5-1.9)
Vagina/vulva	1	3	1.8	(0.4-7.7)	**6.7**	**(3.9-11)**
Prostate	13	30	**1.6**	**(1.1-2.3)**	**0.5**	**(0.5-0.6)**

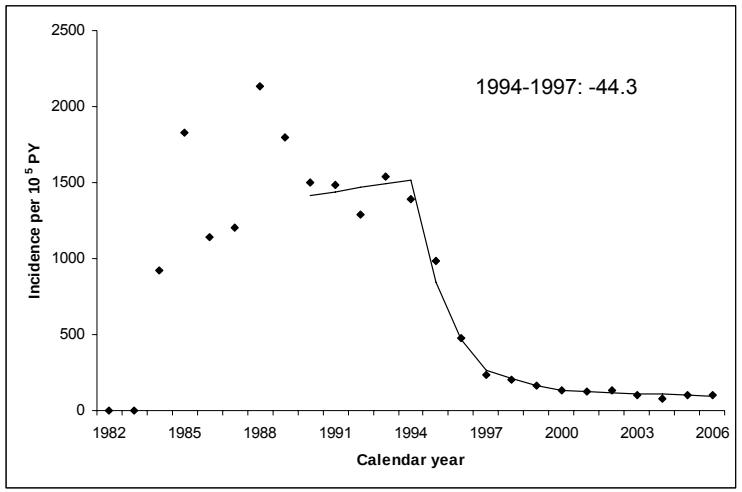
Testis	5	4	1.3	(0.6-2.8)	0.7	(0.5-1.1)
Penis	1	3	3.7	(0.5-29)	**5.0**	**(2.5-8.9)**
Bladder	4	6	1.2	(0.5-2.9)	0.9	(0.6-1.3)
Kidney	6	7	0.9	(0.4-2.1)	0.7	(0.5-1.0)
Brain	4	3	0.7	(0.3-1.9)	0.6	(0.3-1.0)
Thyroid	3	3	1.2	(0.5-3.0)	0.7	(0.4-1.0)
Hodgkin lymphoma	20	41	**2.0**	**(1.3-2.9)**	**11**	**(10-13)**
Nodular sclerosis HL	7	11	1.5	(0.8-2.9)	**5.0**	**(3.7-6.7)**
Mixed cellularity HL	5	13	**2.4**	**(1.2-5.1)**	**21**	**(16-26)**
Other HL	8	17	**2.0**	**(1.1-3.8)**	**15**	**(12-18)**
Myeloma	7	4	**0.5**	**(0.2-1.0)**	0.7	(0.4-1.1)
Lymphocytic leukemia	4	1	0.4	(0.1-1.4)	1.7	(0.8-3.3)
Myeloid/monocytic leukemia	8	7	0.8	(0.4-1.5)	**2.1**	**(1.5-2.9)**
Mesothelioma	1	0	0.2	(0.1-1.1)	0	(0-1.5)
Miscellaneous	70	62	0.8	(0.5-1.1)	**2.6**	**(2.3-2.9)**
Poorly specified	111	30	**0.2**	**(0.2-0.3)**	**3.4**	**(2.9-4.0)**
All non-AIDS cancers	332	448	**1.2**	**(1.0-1.3)**	**1.6**	**(1.6-1.7)**

Table 3 notes

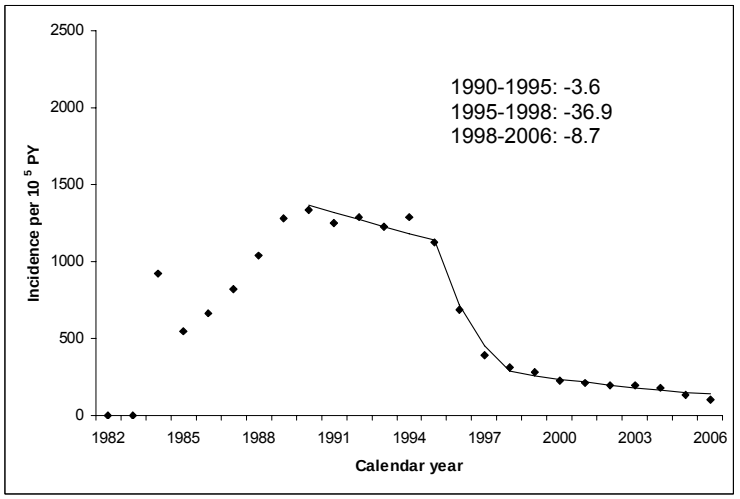
Data are for the combined period 3-10 years after AIDS onset. During the pre-HAART era (calendar years 1990-1995) there were 166,365 person-years of follow-up, and during the HAART era (calendar years 1996-2006) there were 718,401 person-years of follow-up. The rate ratio (RR) compares incidence between the two periods, adjusted for attained age (15-34, 35-44, 45+ years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic), and gender/mode of HIV exposure (males who reported male-to-male sex [MSM] alone or with injection drug use [IDU], all other males, and females). The miscellaneous category includes other cancers with specified topography and histology. The poorly specified category includes cancers of any topography with a poorly specified histology (ICD-O histology codes 8000-8005). The all non-AIDS cancers category excludes AIDS-defining and poorly specified cancers. Bolded values are significant at $P<0.05$. Abbreviations: CI, confidence interval; CNS, central nervous system; HAART, highly active antiretroviral therapy; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; SIR, standardized incidence ratio.

Figure 1. Incidence of selected AIDS-defining malignancies as a function of calendar year

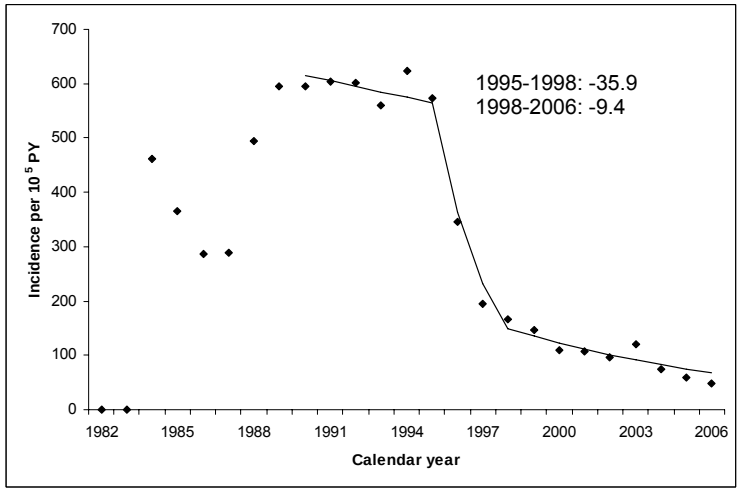
(a) KS



(b) NHL



(c) Diffuse large B-cell NHL



(d) CNS NHL

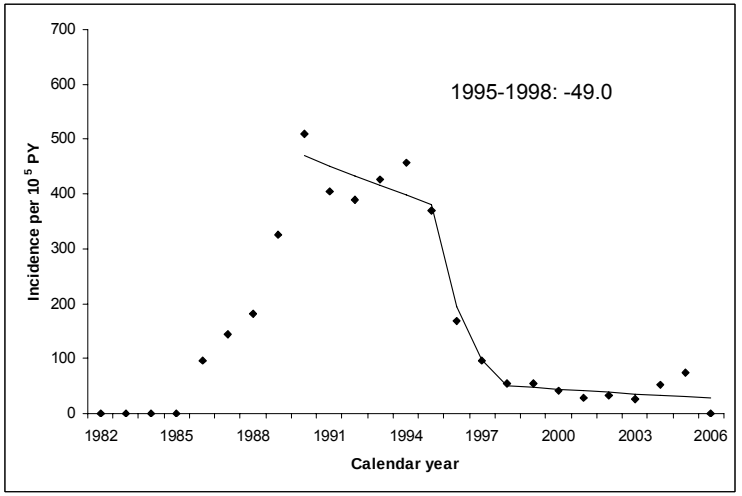
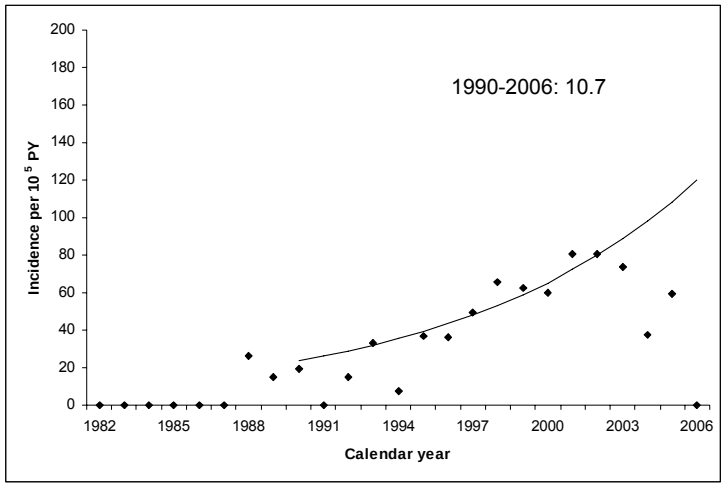
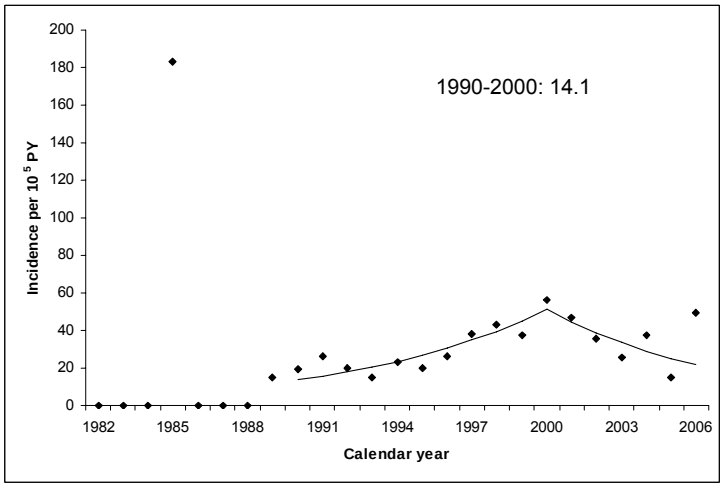


Figure 2. Incidence of selected non-AIDS-defining malignancies as a function of calendar year

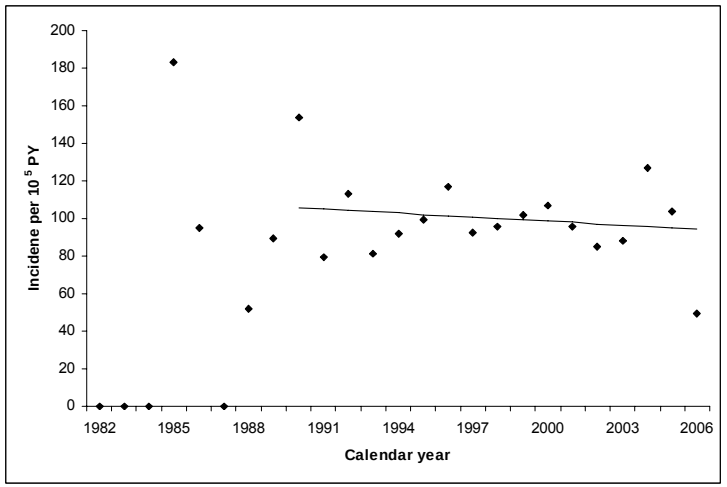
(a) Anal cancer



(b) Hodgkin lymphoma



(c) Lung cancer



(d) All non-AIDS-defining cancers

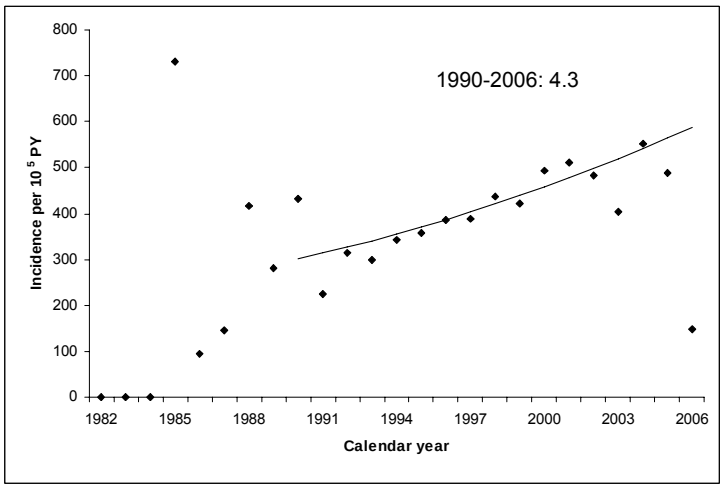


Figure legends

Figure 1. Incidence of selected AIDS-defining malignancies as a function of calendar year. The panels show cancer incidence during the period 3-10 years after AIDS onset, as a function of attained calendar year. The points correspond to the individual year estimates, while the lines correspond to results from the joinpoint regression. Annual percentage change is indicated for calendar years where the change was significantly different from zero *(P*<0.05*)*. Panels correspond to (a) Kaposi sarcoma; (b) non-Hodgkin lymphoma; (c) diffuse large B-cell non-Hodgkin lymphoma; (d) central nervous system non-Hodgkin lymphoma. Abbreviation: PY, person-years.

Figure 2. Incidence of selected non-AIDS-defining malignancies as a function of calendar year. The panels show cancer incidence during the period 3-10 years after AIDS onset, as a function of attained calendar year. The points correspond to the individual year estimates, while the lines correspond to results from the joinpoint regression. Annual percentage change is indicated for calendar years where the change was significantly different from zero *(P*<0.05*)*. Panels correspond to (a) anal cancer; (b) Hodgkin lymphoma; (c) lung cancer; (d) all non-AIDS-defining cancers. Abbreviation: PY, person-years.

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CUMULATIVE INCIDENCE OF CANCER AND CANCER-ATTRIBUTABLE MORTALITY AMONG PERSONS WITH AIDS IN THE UNITED STATES

by

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Written under the direction of

Patricia L. Fleming, Ph.D., M.S.

ABSTRACT OF MANUSCRIPT 2 OF 2

CUMULATIVE INCIDENCE OF CANCER AND CANCER-ATTRIBUTABLE MORTALITY AMONG PERSONS WITH AIDS IN THE UNITED STATES

Dissertation Director:

Patricia L. Fleming, Ph.D., M.S.

ABSTRACT

Background: As persons with acquired immunodeficiency syndrome (AIDS) live longer due to highly active antiretroviral therapy (HAART, widely available in the United States since 1996), cancer risk and the fraction of deaths attributable to cancer may increase.

Methods: Data from a population-based record linkage study of persons with AIDS (1980-2006) were used to identify cancers and deaths in 372,364 subjects. We used competing risk methods to determine cumulative incidence and Cox regression to estimate cancer-attributable mortality across 3 calendar periods (AIDS onset in 1980-1989, 1990-1995, and 1996-2006).

Results: Cumulative incidence of AIDS-defining cancer (ADC) declined across AIDS onset calendar periods (8.7% to 6.4% to 2.1%). Cumulative incidence of non-AIDS-defining cancer (NADC) increased from 0.86% to 1.1% with no significant change thereafter (1.0%, 1996-2006). However, incidence of some site-specific NADCs (anal cancer, Hodgkin lymphoma, liver cancer and lung cancer) increased. Among those with AIDS and cancer, cancer-attributable mortality increased to 88.3% (ADC) and 87.1% (NADC) during 1996-2006, and

population-attributable NADC mortality increased to 2.3% (1996-2006). Population-attributable ADC mortality decreased from 6.3% (1990-1995) to 3.9% (1996-2006).

Conclusions: Dramatically declining incidence of ADCs and increases in some NADCs were noted. Most deaths among persons with AIDS and cancer are attributable to their cancer, and an increasing fraction of all deaths among persons with AIDS are attributable to NADC, indicating the need for cancer treatment and prevention.

CUMULATIVE INCIDENCE OF CANCER AND CANCER-ATTRIBUTABLE MORTALITY AMONG PERSONS WITH AIDS IN THE UNITED STATES

Introduction

Mortality among human immunodeficiency virus (HIV)-infected persons declined dramatically in the U.S. beginning in 1996, following widespread use of highly active antiretroviral therapy (HAART).[1-3] Despite improved overall survival, HIV-infected persons have elevated cancer risk, particularly with late-stage HIV infection (i.e., acquired immunodeficiency syndrome [AIDS]). Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), and cervical cancer are considered AIDS-defining cancers (ADCs).[4] HIV-induced immune suppression leading to poor control of oncogenic viral infections plays an important role in the development of KS (due to KS-associated herpesvirus) and NHL (due to Epstein Barr virus).[5] Cervical cancer is caused by human papillomavirus.[6] HIV-infected persons also have an elevated risk for other malignancies (i.e., non-AIDS-defining cancers [NADCs]), due to a high prevalence of additional viral coinfections (e.g., liver cancer caused by hepatitis C virus) and exposure to other carcinogens (e.g., lung cancer caused by tobacco).[7]

Trends in the risk of ADCs and NADCs among HIV-infected persons have been previously described.[8-11] Prior studies have measured cancer risk in terms of incidence (e.g., rate per 100,000 person-years, or standardized to the general population), which reflects instantaneous risk and is appropriate for considering the effects of various etiologic factors or treatment (e.g., HAART) on the

development of cancer. However, cancer incidence does not translate directly into cumulative risk, that is, the proportion of people with AIDS who will develop cancer over a specified time period. Cumulative incidence reflects both cancer incidence and the occurrence of death, which is a competing event that precludes the occurrence of cancer.[12] As persons with AIDS live longer, their cumulative incidence of other diseases, including cancer, would be expected to increase as they contribute more person-time at risk to the development of these diseases.

As deaths among HIV-infected people decline, especially deaths due to AIDS, a larger fraction of remaining deaths may be attributed to cancer. Some studies which evaluated causes of death, indicated that deaths due to cancer may be increasing in the HAART era.[13-15] However, it is difficult to determine a single cause of death in persons with HIV/AIDS, many of whom have multiple medical conditions.[16] Clinicians may inaccurately ascribe death to cancer, when AIDS or another illness is actually responsible.

In the present study, we determined cumulative incidence of ADC and NADC among persons with AIDS using competing risk models that accounted for mortality. In addition, statistical modeling of mortality data was used to estimate the fraction of deaths among persons with AIDS attributable to cancer. The goals of this study were to quantify the burden of cancer-related events (occurrence of cancer, death due to cancer) among persons with AIDS and to evaluate changes in these outcomes over time relative to widespread HAART use.

Methods

Study design

The HIV/AIDS Cancer Match Study is a population-based registry linkage study of persons with HIV or AIDS diagnosed between 1980 and 2008 from 15 U.S. state and metropolitan regions.[8] Following linkage, only de-identified data are retained for analyses. Institutional review boards at participating sites approved the study.

We constructed a cohort from the HIV/AIDS Cancer Match Study to evaluate cancer risk and cancer-attributable mortality. The cohort was restricted to include cancers occurring at the start of the fourth month after AIDS onset and after, since cancer incidence in first 3 months after AIDS is inflated because of the extensive evaluation of clinical signs and symptoms associated with AIDS.[9] AIDS onset was defined using the 1993 Centers for Disease Control and Prevention definition.[4] Of N=574,242 eligible persons with AIDS, individuals who had any cancer reported to the cancer registry, or an ADC reported to the HIV/AIDS registry, before 4 months after AIDS onset (N=33,374 and N=18,107, respectively) were excluded. Persons whose observation time ended before month 4 (N=128,831) were also excluded as they contributed no cancer information, as well as persons whose follow-up for cancer began after month 4 (N=16,743) in order to make the cohort uniform at baseline. In addition, persons diagnosed with AIDS prior to 1980 (N=7) and children aged less than 14 years

(N=4,816) were excluded, yielding a cohort of adults and adolescents with AIDS who were cancer-free at the start of month 4 after AIDS onset (N=372,364).

Information on invasive cancers was obtained from cancer registries, and malignancies were coded according to the *International Classification for Diseases for Oncology*.[17] Cancers were categorized by site and histology using a modification of the Surveillance, Epidemiology, and End Results (SEER) program's "site recode with Kaposi sarcoma and mesothelioma".[10;18] Only first cancers were considered. Vital status information was obtained from AIDS registries at the time of the linkage.

Statistical methods

Estimating cumulative incidence of cancer

We classified subjects according to calendar year of AIDS onset: 1980-1989 (no or limited availability of antiviral therapy), 1990-1995 (monotherapy and/or dual therapy) and 1996-2006 (HAART). Nonparametric competing risk time-to-event methods were used to evaluate the cumulative incidence of 3 competing outcomes: death, ADC, and NADC. Competing risks occur when one event precludes the other outcome(s) from occurring or being observed. The first occurrence of any of the outcomes was evaluated. In separate models, we obtained the estimate of cumulative incidence at time *t* by summing the products of the overall Kaplan-Meier survival estimate and a nonparametric estimate of the cause-specific hazard function for the outcome of interest (death, ADC, or NADC) over all observed time points just prior to time *t*.[12;19] The competing risk

approach differs from the usual Kaplan-Meier estimates, which simply censor people who remain event-free, resulting in a biased estimate of the probability of the event of interest actually being observed when events are not independent.

Observation began at the start of month 4 after AIDS and stopped at the event of interest, a competing event, or administrative censoring (last follow-up for cancer from the cancer registry or death according to the AIDS registry, whichever occurred first). A similar approach was used to estimate cumulative incidence of each ADC and the major NADCs associated with HIV infection (cancers of the anus, liver, and lung, and Hodgkin lymphoma). Cumulative incidence at 60 months of follow-up (5 years after AIDS onset) and corresponding 95% confidence intervals (95% CIs) were calculated. Five-year cumulative incidence estimates were compared using a t-test, evaluating whether incidence changed for persons diagnosed with AIDS during 1980-1989, 1990-1995, and 1996-2006. For selected cancers, cumulative incidence at 120 months (10 years) of follow-up after AIDS onset was also compared.

Estimating cancer-attributable mortality

To determine mortality due to cancer, we calculated (1) the fraction of deaths attributable to cancer among persons with cancer (attributable risk [AR]) and (2) the fraction of deaths attributable to cancer among all persons with AIDS (population attributable risk [PAR]).[20] The cohort was divided into the same three groups according to calendar year of AIDS onset, and mortality was evaluated over a 5-year (60 months) period beginning at month 4 after AIDS onset.

Analyses were conducted separately to assess mortality attributable to ADC, NADC, and any cancer combined.

A difficulty in applying standard formulae for AR and PAR is that they evaluate individuals at a single time point, when all subjects can be unambiguously classified with respect to the exposure and outcome. To account for the fact that cancers and deaths both continued to occur throughout 5 years of follow-up, the person-time was divided into 10 intervals of 6-month duration. Subjects were classified according to their cancer status at the start of each interval. Next, for each interval a Cox regression model was fitted to measure the association between presence of cancer (at or before the start of the interval) and death during the interval, adjusted for gender, race/ethnicity and age. For each interval, AR=(HR-1/HR) and PAR=[P_e*(HR-1)/P_e*(HR-1)+1] were obtained, where the HR was the adjusted hazard ratio from the Cox model and P_e was the proportion of subjects with cancer (i.e., exposed) at or before the interval. Overall AR and PAR estimates were derived for the entire 60 months of follow-up by multiplying the interval-specific AR and PAR estimates by the interval-specific number of deaths in persons with cancer or the interval-specific total deaths, respectively; summing these interval-specific attributable deaths across the intervals; and expressing the total attributable deaths as a fraction of all deaths in persons with cancer (AR) or all deaths in the cohort (PAR).

Variances for AR and PAR estimates were derived using the delta method,[21] and estimates were compared for subjects diagnosed with AIDS during 1980-1989, 1990-1995, and 1996-2006 using a two-sided t-test. We used

SAS, version 9.1 (SAS Institute, Cary, North Carolina) for the competing risk and Cox models and R software to implement the delta method. For both cumulative incidence and attributable mortality analyses, *P*-values <0.05 were considered significant.

Results

Demographic characteristics of the 372,364 people included in the study are presented in Table 1. The proportion of males declined from 88.0% (1980-1989) to 74.7% (1996-2006) and the proportion of non-Hispanic whites decreased, while the proportion of non-Hispanic blacks and Hispanics increased over time. Of the major categories of HIV exposure, the proportion of men reporting male-to-male sex declined from 59.2% in 1980-1989 to 52.8% in 1996-2006, and the proportion reporting heterosexual contact increased from 3.8% to 6.7% during the same periods. Reporting of $CD4^+$ T-lymphocytes was uncommon until the 1990s, and the CD4 count at AIDS onset increased slightly over time (median 110 vs. 117 cells/uL among persons diagnosed with AIDS during 1990-1995 and 1996-2006, respectively; Table 1).

Based on competing risk models, cumulative incidence of death (as a first event, prior to cancer) rose steeply immediately following AIDS onset for persons diagnosed during 1980-1989 and 1990-1995 (Table 2). The increase was less dramatic for those with AIDS onset during 1996-2006. Five-year cumulative incidence of death declined significantly across AIDS calendar periods, from 75%

(1980-1989) to 52% (1990-1995) to 19% (1996-2006). Significant declines were also noted at 120 months of follow-up.

Similarly, cumulative incidence of ADCs increased steeply after AIDS onset for persons diagnosed during 1980-1989 and 1990-1995, and to a lesser extent, during 1996-2006 (Figure 1A). Five-year cumulative incidence of ADC declined significantly with AIDS calendar time: 8.7% during 1980-1989, 6.4% during 1990-1995, 2.1% during 1996-2006) (Table 2). Similar declines for ADCs were noted at 120 months (Figure 1A).

Kaposi sarcoma was the most common ADC during 1980-1989 (71%) and 1990-1995 (58%); however, during 1996-2006 NHL accounted for a majority of ADC events (54%) (Table 2). Cumulative incidence of KS declined across the three calendar periods of AIDS onset. For NHL, cumulative incidence increased from 2.3% among persons with AIDS onset during 1980-1989 to 2.6% during 1990-1995 and subsequently declined to 1.2% among persons diagnosed with AIDS during 1996-2006. The 5-year cumulative incidence of cervical cancer increased from 0.16% among women diagnosed with AIDS during 1980-1989 to 0.28% during 1990-1995 and to 0.33% during 1996-2006, although the latter increase was not significant (Table 2). Cumulative incidence at 120 months of follow-up did not change appreciably over time (0.42% among women with AIDS onset during 1996-2006).

In contrast, cumulative incidence of NADCs overall increased significantly from 1980-1989 to 1990-1995 (from 0.86% to 1.1%); no significant change was apparent among persons diagnosed with AIDS during 1996-2006 (1.0%) (Figure

1B and Table 2). Notably, a progressive significant increase in 5-year cumulative incidence was observed across the three successive calendar periods of AIDS onset for several site-specific NADCs (Figure 2 and Table 2). These cancers were anal cancer (cumulative incidence increasing from 0.03% to 0.08% to 0.15%), Hodgkin lymphoma (0.04% to 0.10% to 0.17%), liver cancer (0.01% to 0.03% to 0.08%), and lung cancer (0.14% to 0.28% to 0.37%). At 120 months of follow-up, cumulative incidence of Hodgkin lymphoma (P=0.03) and lung cancer (P=0.02) also increased among persons diagnosed with AIDS during 1996-2006 relative to 1990-1995 (Figures 2B and 2D).

Mortality rates in people with and without a cancer diagnosis are presented in Table 3. Mortality following an ADC was very high among those with AIDS onset in 1980-1989 (1503 per 1000 person-years) and declined in people with AIDS onset in later periods. In comparison, mortality rates among subjects who were ADC-free were markedly lower and declined more strongly with AIDS calendar time. As a result, among persons with an ADC who died, the AR (i.e., proportion of deaths attributable to their ADC) increased significantly across AIDS calendar time from 68.6% during 1980-1989 to 77.8% during 1990-1995 to 88.3% during 1996-2006 (Table 3). Nonetheless, during the two most recent calendar periods of AIDS onset, the PAR (i.e., proportion of all deaths among people with AIDS attributable to ADC) declined significantly from 6.3% (1990-1995) to 3.9% (1996-2006).

Mortality following a NADC was also highest among persons with AIDS onset during 1980-1989 (1531 per 1000 person-years) (Table 3). Mortality was

much lower among persons who were NADC-free and declined across calendar periods from 465 per 1000 person-years (1980-1989) to 58 per 1000 person-years (1996-2006). Among persons with NADC, the AR increased significantly over AIDS calendar time from 71.9% (1980-1989) to 73.9% (1990-1995) and 87.1% (1996-2006). In contrast to the findings for ADC, the PAR related to NADC significantly increased with AIDS onset calendar periods (0.5% in 1980-1989, 0.8% in 1990-1995, and 2.3% in 1996-2006; Table 3).

Finally, mortality rates and estimates of deaths attributable to cancer overall (ADC and NADC combined) are shown in Table 3. Similar to patterns noted for ADC and NADC, among people with any cancer, the AR related to their cancer increased across calendar periods of AIDS onset. While the overall mortality attributable to any cancer was similar across calendar year of AIDS onset (PARs 6.0-6.9%), over time a larger fraction of the deaths were attributed to NADC.

Discussion

In this large and nationally representative cohort of people with AIDS, we observed significant declines in the cumulative incidence of ADC over time, consistent with broadening access to improved HIV therapies, including HAART (widely available since 1996). In striking contrast, however, we noted a rise in the cumulative incidence of NADC, including malignancies that occur with heightened frequency among HIV-infected people. Of further note, with improvements in overall mortality, a greater fraction of deaths in people with an

ADC or NADC were attributable to their cancer. Finally, the fraction of all deaths attributable to NADC (i.e., the PAR) increased for people diagnosed with AIDS in the HAART era.

Major declines in mortality attributable to improved antiretroviral therapies are well documented.[1;2] HAART is effective in controlling HIV replication, leading to improved immune function and prolonged survival.[3] Declines in mortality among HIV-infected people were also observed in the U.S. prior to 1996, presumably due to increasing use of less potent antiretroviral regimens and better prophylaxis against opportunistic infections.[22] These strong trends in mortality required the application of a competing risk framework to assess the cumulative incidence of cancer. Although more familiar, the Kaplan-Meier method would have been inappropriate, as it considers people who die to be censored (i.e., unobserved but still at risk for cancer). The cumulative incidence estimates in the present study correspond to the probability of observing cancer while a person with AIDS was still alive, are useful in assessing cancer risk for patients and clinicians, and can inform public health practice as a measure of cancer burden in the AIDS population.

Risk of the two major ADCs, KS and NHL, is elevated in the presence of immune suppression, and dramatic declines in the cumulative incidence of KS and NHL over time were demonstrated, consistent with partial immune restoration associated with HAART.[23-25] Five-year cumulative incidence of KS and NHL declined 78% and 85%, respectively, among persons diagnosed with AIDS during diagnosed during 1996-2006 (HAART era) compared with those

diagnosed in the 1980s. However, NHL remained the most common cancer during the most recent calendar period of AIDS. The continued occurrence of both KS and NHL suggests the need for increases in access and adherence to HAART.[26;27] Among women, the cumulative incidence of cervical cancer changed little with the widespread availability of HAART.

Overall, cumulative incidence of NADCs was low, but increased over time. This trend largely reflects the decline in mortality, which has allowed people with AIDS to live long enough to develop cancer. In particular, cumulative incidence of anal and liver cancers increased among persons diagnosed with AIDS in the HAART era compared with earlier periods. It is possible that HAART-associated immune restoration does not influence the natural history of infections with human papillomavirus (anal cancer) or hepatitis C and B viruses (liver cancer).[28-30] In addition, an increase in the cumulative incidence of Hodgkin lymphoma in the HAART era was noted. Some studies,[9;31] although not all,[32] have reported an increase in Hodgkin lymphoma incidence in the HAART period, which may reflect the complex relationship between immunosuppression and development of this malignancy.[33] A rise over time in the cumulative incidence of lung cancer was also observed. The excess risk of lung cancer is partly due to a high prevalence of smoking,[34] but chronic pulmonary inflammation or repeated lung infections in HIV-infected people may also be involved.[35]

The presented cumulative incidence estimates accurately reflect changes in cancer risk within the overall cohort over time. We conducted additional stratified analyses to estimate cumulative incidence of ADC and NADC within

separate groups defined by gender/mode of HIV transmission (MSM, other males and females) and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other/unknown). Results were consistent with overall trends shown in Table 2, indicating that the overall trends in cumulative incidence were not due to demographic changes within the cohort (APPENDIX IV). Only a multivariable cumulative incidence model can control for the joint effect of these changes over time, and future analyses may employ such a strategy.

The attributable mortality results provide further context on the impact of cancer in this population. Although mortality among people with AIDS has declined dramatically over time, mortality has fallen less rapidly among those who also have cancer, and mortality rates among people with AIDS and cancer remain very high. As a result, cancer now accounts for the vast majority of deaths among people with AIDS and cancer. These results highlight that improved treatment of cancers among persons with AIDS would have a major impact on survival. Both AIDS-related immunosuppression, and interactions between chemotherapy agents and HAART regimens, can adversely limit the effectiveness of cancer-directed treatment. Because individual treatment centers may see few cases of cancer among persons with HIV/AIDS, multi-center consortia are needed to comprehensively evaluate cancer treatment protocols in this population.

Finally, the overall contribution of cancer to mortality among people with AIDS (i.e. the population attributable risk) depends on the frequency of occurrence of cancer, mortality following cancer, and mortality among people

who are cancer-free. For ADCs, the decline in PAR over time is explained by the dramatic decline in the cumulative incidence of these malignancies. In contrast, the cumulative incidence of NADC increased over time, contributing to the increase in the PAR from 0.5% among persons diagnosed with AIDS during 1980-1989 to 2.3% among persons diagnosed with AIDS during 1996-2006. For comparison, 5% of deaths among persons with AIDS in New York City (1999-2004), had cancer listed as the underlying cause,[13] and a study of HIV-infected persons in Europe (1996-2006) found that 8% of deaths were attributable to cancer.[15] Our estimate of overall cancer-attributable mortality is lower than in the prior studies, perhaps because subjects with cancer during the AIDS onset period were excluded in order to provide meaningful estimates of the cumulative incidence of ADC and NADC. Additionally, the European study included people who had not yet developed AIDS and so had fewer AIDS-related deaths (and therefore a greater proportion of cancer-related deaths). Heterogeneity of results across studies can also be explained by methodological differences (i.e., use of statistical methods to calculate the PAR vs. review of cause of death information such as on a death certificate) and reflect the challenge in accurately determining a single cause of death in patients with multiple medical problems.[16]

Strengths of this study include its large size and inclusion of major U.S. areas affected by the HIV/AIDS epidemic. The present estimates of cumulative incidence of cancer and cancer-attributable mortality are therefore likely generalizable to the U.S. AIDS population. A limitation is that only persons with AIDS were evaluated, who comprise a subset of the overall HIV-infected

population. The cumulative incidence of most NADCs would be expected to be higher in HIV-infected people without AIDS, because the competing risk of death is lower in this group than among people with AIDS. Because of incomplete ascertainment of HIV transmission category and CD4 count during 1990-1995, and changes in surveillance practices (i.e.: the 1993 case definition),[4] interpreting trends in these characteristics requires statistical adjustments which we were unable to conduct. For HIV transmission category, adjustments are made at the national level which redistribute persons with unknown/missing risk factors to other categories, using multiple imputation methods.[36] While the data presented in Table 1 are unadjusted, the trends in HIV transmission category by calendar period of AIDS onset presented are consistent with national adjusted estimates.[36] With regards to CD4 count data, ascertainment and reporting of CD4 counts was not systematic or consistently done in the early to mid 1990s; therefore, any trend in CD4 count data should be interpreted with caution. Also, individual-level data were lacking on important cancer co-factors such as HAART use, infection with oncogenic viruses, and smoking, which influence cancer risk.

The change in the 1993 AIDS case definition resulted in an increase in cases reported during the months immediately following implementation; most of which were reported because they met the new immunologic criteria for AIDS (CD4 count <200 cells/uL).[37] It is difficult to determine the impact of this influx of AIDS cases on our findings regarding cancer risk. However, we hypothesize that any potential impact would be limited to our estimates of cumulative incidence of the AIDS-defining cancers associated with immune suppression (i.e.: KS and

NHL). It is reasonable to suggest that persons diagnosed with a CD4 counts <200 cells/uL but not much lower, would have lower risk of KS and NHL, and also of overall mortality, as risks of these outcomes increases with worsening immune suppression. The estimates we present of cancer cumulative incidence among persons diagnosed with AIDS during 1990-1995 would be most impacted by this change. It is possible that both mortality and KS and NHL events are under-estimated due to the large influx of persons with CD4 counts <200 cells/uL in 1993 and 1994. This change may have distorted our findings in a number of ways. First, the change may have exaggerated declines in cumulative incidence among persons diagnosed with AIDS during 1990-1995 compared to those diagnosed during 1980-1989, because some of the years in the 1990-1995 period used the new case definition (1993 and onwards). Secondly, the change in the 1993 AIDS case definition may have also exaggerated the effect of widespread HAART use, by exaggerating declines in cumulative incidence among persons diagnosed with AIDS during 1996 and onwards relative to those diagnosed during 1990-1995. Again, this is because part of 1990-1995 used the old AIDS case definition (pre-1993, which did not allow for immunologically identified cases). Similarly, changes in AIDS surveillance practices may have had an analogous impact on the trends we noted in ADC-attributable mortality. However, our analyses and conclusions reflect the composite effects of declines in mortality, and ADC cumulative incidence, as well as the impact of the change in surveillance practices, among persons diagnosed with AIDS during the three calendar periods of observations. Changing AIDS surveillance practices and

modifications to the AIDS case definition make adjustments to our data complicated, and any such adjustments are beyond our expertise and the scope of this project.

Patterns of cancer incidence and cancer-attributable deaths among persons with AIDS in the United States are changing in the HAART era. Dramatic declines in the cumulative incidence of ADCs were noted along with an increase in the cumulative incidence of some NADCs, including those for which incidence is higher than in the general population (cancers of the anus, liver, and lung, and Hodgkin lymphoma). Among people with AIDS who develop cancer, their malignancy is the predominant cause of death, pointing to a pressing need for more effective cancer treatment in this population. Further, NADCs account for a small but growing proportion of all deaths among persons diagnosed with AIDS in the HAART era. As HIV infection is increasingly considered with chronic disease management paradigms, greater attention should be focused on cancer screening and prevention strategies.

Table 1. Demographic characteristics of persons with AIDS in the United States, 1980-2006 (N=372,364)

	AIDS Diagnosis Calendar Period					
Characteristic	**1980-1989**		**1990-1995**		**1996-2006**	
Total No.	51575		171932		148857	
Sex, n (%)						
Male	45395	(88.0)	139166	(80.9)	111128	(74.7)
Female	6180	(12.0)	32766	(19.1)	37729	(25.3)
Age in years at AIDS onset, n (%)						
15-29	10817	(21.0)	28742	(16.7)	20718	(13.9)
30-39	25185	(48.8)	79819	(46.4)	62518	(42.0)
40-49	11304	(22.0)	46727	(27.2)	46688	(31.4)
50+	4269	(8.2)	16644	(9.7)	18933	(12.7)
Median	35		37		38	
Race/ethnicity, n (%)						
Non-Hispanic white	26007	(50.4)	68007	(39.6)	42571	(28.6)
Non-Hispanic black	16296	(31.6)	66093	(38.4)	72329	(48.6)
Hispanic	8764	(17.0)	35907	(20.9)	32106	(21.6)
Other/unknown	508	(1.0)	1925	(1.1)	1851	(1.2)
Mode of HIV exposure, n (%)[a]						
MSM	28497	(59.2)	75401	(51.3)	52810	(52.8)
IDU	14194	(29.5)	52850	(35.9)	33423	(33.4)
MSM and IDU	3602	(7.5)	10553	(7.2)	7117	(7.1)
Heterosexual	1826	(3.8)	8327	(5.7)	6649	(6.7)
CD4 count at AIDS onset (cells/uL), n (%)						
0-99	1410	(2.7)	55781	(32.4)	58549	(39.3)
100-199	1778	(3.4)	46609	(27.1)	52116	(35.0)
200+	947	(1.9)	17710	(10.3)	21505	(14.5)
Missing	47440	(92.0)	51832	(30.2)	21505	(11.2)
Median	144		110		117	

Table 1 notes
Abbreviations: MSM, male-to-male sex; IDU, injection drug use.
[a] Column percentages for mode of HIV exposure are reported for the four most common modes of exposure excluding persons in the 'other/unknown' category (most subjects in the other/unknown category had unknown rather than other known mode of transmission).

Table 2. Cumulative incidence of death, AIDS-defining cancers, and non-AIDS-defining cancers, as first-events, among persons with AIDS in the United States, 1980-2006

Occurrence of outcome as a first-event	Cumulative incidence at five years of follow-up after AIDS onset								
	AIDS onset in 1980-1989			AIDS onset in 1990-1995			AIDS onset in 1996-2006		
	No. of events	Percentage with outcome	95% CI	No. of events	Percentage with outcome	95% CI	No. of events	Percentage with outcome	95% CI
Death	41217	75	74, 75	97926	**52**	**52,53**	22189	**19**	**19, 20**
AIDS-defining cancer	4781	8.7	8.5, 8.9	11871	**6.4**	**6.3, 6.5**	2474	**2.1**	**2.0, 2.2**
Kaposi sarcoma	3405	6.3	6.1, 6.5	6834	**3.8**	**3.7, 3.9**	1056	**0.89**	**0.84, 0.95**
Non-Hodgkin lymphoma	1355	2.3	2.2, 2.5	4917	**2.6**	**2.5, 2.6**	1326	**1.2**	**1.1, 1.2**
Cervical cancer[c]	21	0.16	0.07, 0.26	120	**0.28**	**0.23, 0.34**	92	0.33	0.26, 0.40
Non-AIDS-defining cancer	546	0.86	0.78, 0.93	2440	**1.1**	**1.0, 1.1**	1151	1.0	1.0, 1.1
Anal cancer	22	0.03	0.01, 0.04	310	**0.08**	**0.07, 0.10**	163	**0.15**	**0.12, 0.20**
Hodgkin lymphoma	24	0.04	0.02, 0.06	266	**0.10**	**0.09, 0.12**	195	**0.17**	**0.15, 0.20**
Liver cancer	14	0.01	0.00, 0.02	117	**0.03**	**0.03, 0.04**	90	**0.08**	**0.06, 0.10**
Lung cancer	108	0.14	0.11, 0.18	715	**0.28**	**0.26, 0.31**	408	**0.37**	**0.33, 0.41**

Table 2 notes
Abbreviation: CI, confidence interval
Cumulative incidence was calculated using competing risk methods at 60-months of follow-up, expressed as a percentage (%) of people with the specified outcome. The cumulative incidence estimates presented are of each outcome, as a first-event. When outcome is less than 1%, we present the percentage to 2-significant digits.
[a] Cumulative incidence estimates during 1990-1995 were compared to those during 1980-1989 via a two-sided t-test. Bolded values indicate a significant difference at $P<0.05$.
[b] Cumulative incidence estimates during 1990-1995 were compared to those during 1996-2006 via a two-sided t-test. Bolded values indicate a significant difference at $P<0.05$.
[c] Analyses were restricted to women.

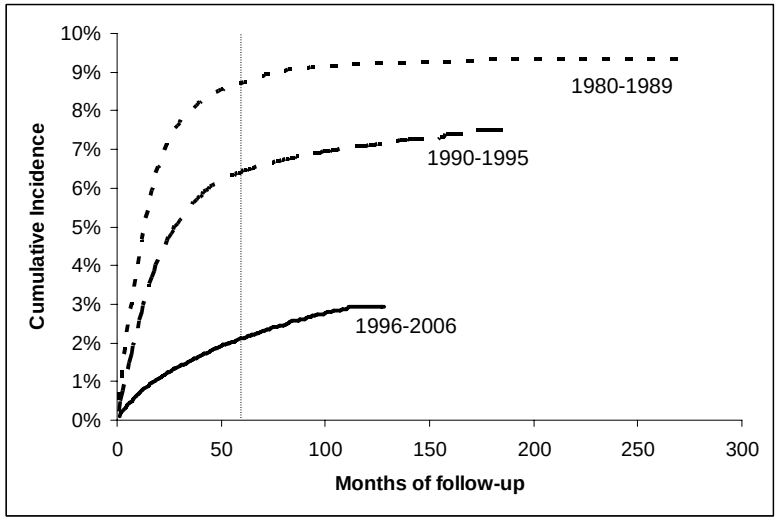
Table 3. Cancer-attributable mortality among persons with AIDS in the United States, 1980-2006

	Calendar Year of AIDS Onset					
	1980-1989		1990-1995[a]		1996-2006[b]	
Cancer type	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
AIDS-defining cancer						
Mortality per 1000 person-years	1503	1451, 1555	873	852, 894	402	376, 430
Cancer-free, mortality per 1000 person-years	479	474, 483	218	217, 220	59	58, 60
Attributable risk, %	68.6	67.4, 69.7	**77.8**	**77.2, 78.3**	**88.3**	**87.5, 89.2**
Population attributable risk, %	6.3	6.0, 6.6	6.3	6.1, 6.5	**3.9**	**3.6, 4.2**
Non-AIDS-defining cancer						
Mortality per 1000 person-years	1531	1337, 1744	680	638, 724	440	406, 477
Cancer-free, mortality per 1000 person-years	465	461, 469	212	211, 213	58	57, 59
Attributable risk, %	71.9	68.1, 75.8	**73.9**	**72.3, 75.6**	**87.1**	**85.9, 88.1**
Population attributable risk, %	0.5	0.4, 0.5	**0.8**	**0.8, 0.9**	**2.3**	**2.1, 2.5**
Any cancer						
Mortality per 1000 person-years	1504	1455, 1555	843	825, 862	417	396, 439
Cancer-free, mortality per 1000 person-years	480	475, 485	219	218, 221	59	58, 60
Attributable risk, %	68.7	67.6, 69.9	**77.1**	**76.5, 77.6**	**87.6**	**87.1, 88.2**
Population attributable risk, %	6.7	6.3, 7.0	**6.9**	**6.8, 7.1**	**6.0**	**5.7, 6.4**

Table 3 notes
Abbreviation: CI, confidence interval
[a] Attributable risk and population attributable risk estimates during 1990-1995 were compared to those during 1980-1989 via a two-sided t-test. Bolded values indicate a significant difference at $P<0.05$.
[b] Attributable risk and population attributable risk estimates during 1990-1995 were compared to those during 1996-2006 via a two-sided t-test. Bolded values indicate a significant difference at $P<0.05$.

Figure 1. Cumulative incidence of AIDS-defining and non-AIDS-defining cancer among persons with AIDS in the United States, 1980-2006

(A) AIDS-defining cancer



(B) Non-AIDS-defining cancer

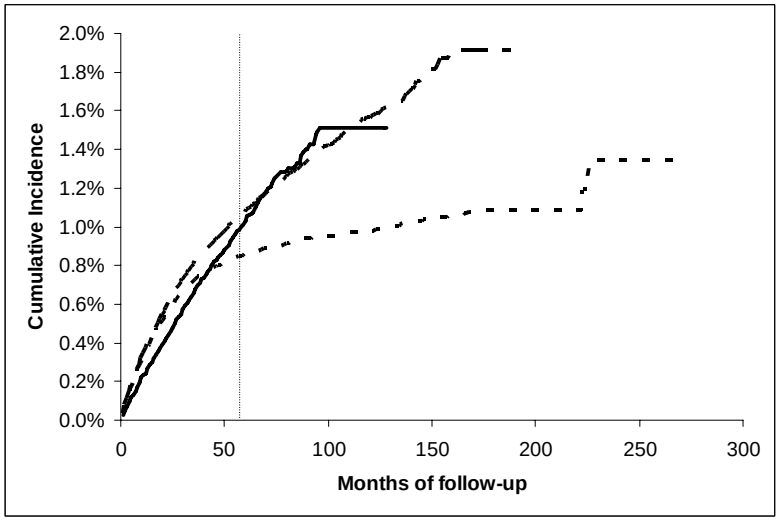
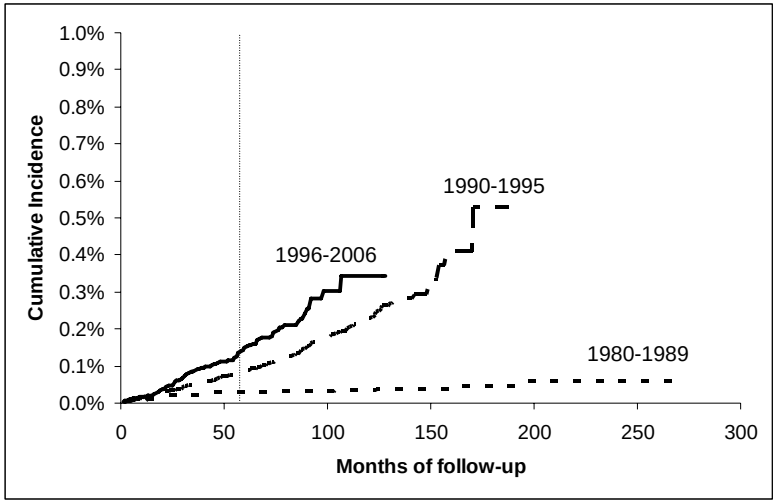
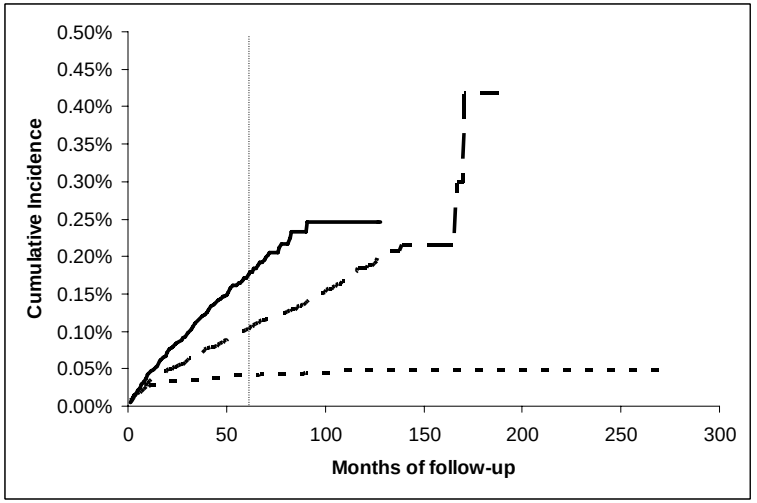


Figure 2. Cumulative incidence of selected Non-AIDS-defining cancers among persons with AIDS in the United States, 1980-2006

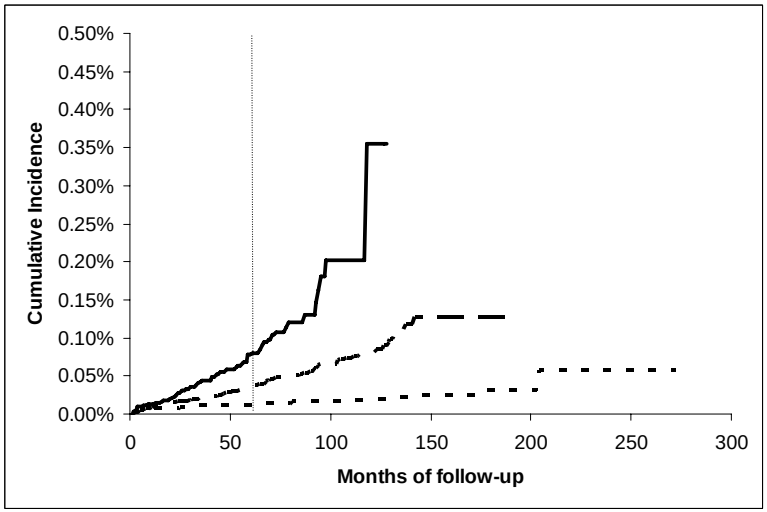
(A) Anal cancer



(B) Hodgkin lymphoma



(C) Liver cancer



(D) Lung cancer

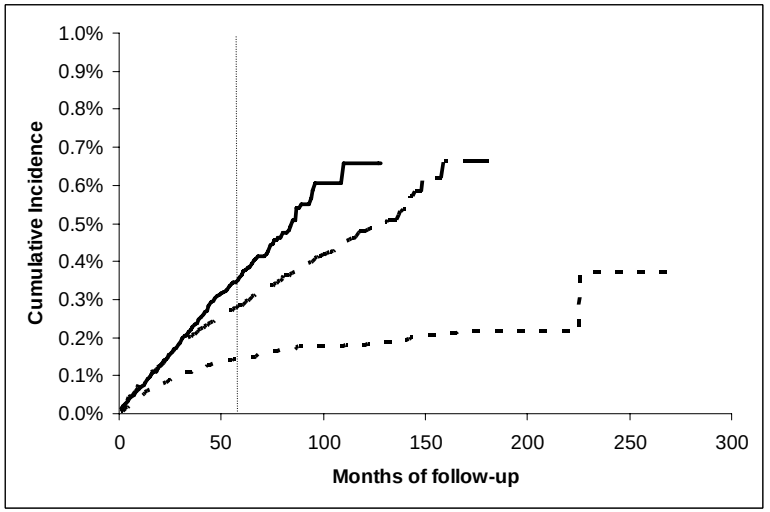


Figure legends

Figure 1. Cumulative incidence of cancer (as a first-event) among persons with AIDS in the United States. Results are shown for death (panel A), AIDS-defining cancers (panel B), and non-AIDS-defining cancers (panel C). Results are stratified by calendar year of AIDS onset: 1980-1989 (dotted line), 1990-1995 (dashed line), 1996-2006 (solid line). Cumulative incidence was estimated using competing risk time-to-event methods and is expressed as a percentage. Follow-up time is measured beginning at 4 months after AIDS onset. The gray vertical line indicates cumulative incidence estimates compared at month 60 of follow-up (5-year cumulative incidence). Vertical scales vary among the panels.

Figure 2. Cumulative incidence of selected non-AIDS-defining cancers (as a first-event) among persons with AIDS in the United States. Results are shown for anal cancer (panel A), Hodgkin lymphoma (panel B), liver cancer (panel C) and lung cancer (panel D). Results are stratified by calendar year of AIDS onset: 1980-1989 (dotted line), 1990-1995 (dashed line), 1996-2006 (solid line). Cumulative incidence was estimated using competing risk time-to-event methods and is expressed as a percentage. Follow-up time is measured beginning at 4 months after AIDS onset. The gray vertical line indicates cumulative incidence estimates compared at month 60 of follow-up (5-year cumulative incidence). Vertical scales vary among the panels.

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CONCLUSION

Survival after an AIDS diagnosis has dramatically increased with widespread HAART use in the U.S.[1;2] Consequently, people living with AIDS today experience increased risks for chronic diseases which often occur later in life, including cancer. While HAART suppresses HIV replication, it does not eradiate HIV infection, and immune suppression persists. The continued occurrence of cancers demonstrates the importance of HIV-associated immune suppression and the increased prevalence of lifestyle-related cancer risk factors in cancer development, among persons with AIDS, in the HAART era.[3-5] This dissertation provided estimates of long-term cancer risk, estimates of the 5-year cumulative incidence of cancer, and estimates of cancer-attributable mortality, relative to widespread HAART use (1996). Such information should be used to inform clinicians caring for persons with AIDS, public health programs providing assistance to persons with AIDS, and researchers investigating the causes and consequences of cancer in this marginalized population.

The following table summarizes results from the research conducted for this dissertation. The first column shows the cancer types of greatest public health importance. Columns 2 and 3 show findings from the first analysis of cancer risk late after AIDS. Column 2 shows the magnitude of standardized incidence ratios during the HAART era (1996-2006) as a measure of risk relative to the general population, and column 3 shows the magnitude of rate ratios assessing changes in cancer incidence in years 3-10 after AIDS, for two calendar

periods of AIDS onset, 1990-1995 (the pre-HAART era) and 1996-2006 (the HAART era). Columns 4-6 display results from the second analysis of cancer cumulative incidence and cancer-attributable mortality during the first 5 years of follow-up. Column 4 shows the magnitude of change in cancer cumulative incidence for AIDS onset during the HAART era (1996-2006) compared to AIDS onset during 1990-1995. Columns 5 shows the magnitude of change in the fractions of cancer-attributable deaths (i.e.: attributable risk) compared across the same periods of AIDS onset. The attributable risk represents the fraction of deaths among persons with AIDS and cancer that could be eliminated if cancer were prevented. Column 6 shows the magnitude of change in the population fractions of cancer-attributable deaths (i.e.: population attributable risk), compared across the same calendar periods of AIDS onset. The population attributable risk represents the fraction of deaths among all persons with AIDS (regardless of cancer status) that could be prevented if cancer were eliminated.

Table 1. Summary of major findings regarding cancer risk among persons with AIDS in the HAART era (1996-2006)

Outcome	During years 3-10 after AIDS onset		Up to 5-years of follow-up after AIDS onset		
	Risk relative to the general population during the HAART era	Change in incidence relative to widespread HAART use	Change in cumulative incidence, relative to widespread HAART use, controlling for mortality	Change in attributable deaths relative to widespread HAART use	Change in population attributable deaths relative to widespread HAART use
Any cancer	↑	↓↓↓	-	↑	↓
AIDS-defining cancers	↑↑↑	↓↓↓	↓↓↓	↑	↓
Kaposi sarcoma	↑↑↑	↓↓↓	↓↓↓	-	-
NHL	↑↑	↓↓↓	↓↓	-	-
Cervical cancer	↑	↕	↕	-	-
Non-AIDS-defining cancers	↑	↑	↕	↑↑	↑↑
Anal cancer	↑↑	↑	↑↑	-	-
Hodgkin lymphoma	↑↑	↑	↑↑	-	-
Liver cancer	↑	↕	↑↑	-	-
Lung cancer	↑	↓	↑	-	-

Notes: ↑ significant excess relative to general population or increase over time, ↓ significant deficit relative to general population or decrease over time, ↕ similar to general population or no change over time, - not estimated.
Number of arrows reflects magnitude of increase or decrease relative to general population or the magnitude of change.

We demonstrated significant declines in the incidence of the major AIDS-defining cancers (KS and NHL) relative to widespread HAART use among persons who have survived AIDS for several years. However, persons with AIDS remain at increased risk for these cancers, compared to the general population,

and cancer continues to be an important cause of attributable mortality. We found that during the 10 years after AIDS diagnosis, risk of all non-AIDS-defining cancers combined remained elevated compared to the general population and cumulative incidence of these cancers increased during the HAART era, due to improved survival and thus an increase in the time at risk for cancer. We also demonstrated that among those with non-AIDS-defining cancer who subsequently died, most deaths were attributed to that cancer and that this fraction increased over time. Among the entire population of persons with AIDS, non-AIDS-defining cancers accounted for an increasing fraction of all deaths in the HAART era (population attributable risk). We noted increased risks relative to the general population and increases in cumulative incidence for the following major non-AIDS-defining cancers: cancer of the anus, lung, liver and for Hodgkin lymphoma. Among persons with AIDS in the U.S. during the HAART era, the burden of cancer and cancer-attributable mortality remains substantial. These conclusions are the basis for a number of recommendations to follow.

From a clinical perspective, HIV care providers should continue to monitor their patients for cancer. The findings from these dissertation studies provide the first long-term, population-based estimates of cancer risk among persons with AIDS in the HAART era, and provide additional evidence of the considerable burden of cancer among persons with AIDS. Cancer risk may be heightened further among persons with HIV (and not AIDS), as they experience less AIDS-related mortality; this prolonged survival could provide additional time for the carcinogenic effects of various agents to manifest as cancer. In the anal cancer

model, HPV associated precancer (anal intraepithelial neoplasia) takes years to progress to an invasive tumor; if these early precancerous lesions are present before HIV therapy is initiated, HAART may not slow progression to anal cancer.[6] This model may partially explain the observed increases in anal cancer incidence in our cohort, and others.[6;7] As antiviral therapies for HIV infection evolve, agents which boost immune restoration or are more effective at combating resistant strains of HIV may offer additional immune restorative effects. The role of immune suppression has been well-documented in the natural history of the major AIDS-defining cancers (KS and NHL),[3;8-11] but is unclear for non-AIDS-defining cancers.[12;13] For those cancers strongly associated with immune suppression, advanced HIV therapies could confer additional protection. Two recent studies suggest that earlier initiation of HAART is protective against AIDS and AIDS-related mortality, and earlier therapy may also delay or prevent cancer onset.[14;15]

Additional cancer risk factors may also be addressed in the clinical setting. Smoking cessation and alcohol dependence treatment would substantially decrease risks of lung and liver cancer, respectively. Routine hepatitis B vaccination is recommended for HIV-positive persons,[16] and prevents HBV-related liver cancer. Clinicians should also encourage sexual (condoms, abstinence) and injection drug use (sterile syringes and equipment) harm reduction techniques which would reduce secondary transmission of HIV and possibly oncogenic viruses.[16] Among infection naïve persons, these strategies may prevent acquisition of oncogenic viruses (i.e.: HPV, HBV, and HCV), and

their associated cancers. Routine HPV vaccination is now recommended for 11-12 year old girls and women 13-26 years of age who have not yet been vaccinated or completed the vaccine series.[17] As vaccination coverage levels increase, cohort-specific cervical cancer incidence will decline among vaccinated women, including those with HIV/AIDS. The efficacy of HPV vaccination among HIV-infected people, and in the prevention of anal cancer, is unknown. Of note, anal cancer screening (anal Pap smears to detect anal precancer) among MSM has been found to be cost-effective,[18] and may be cost-effective among other high-risk groups. Widespread screening for anal intraepithelial neoplasia could reduce the burden of anal cancer among persons with HIV/AIDS.

These findings also have implications for cancer treatment specialists. Although cancer remains an uncommon health event among persons with AIDS, optimized treatment protocols are needed for the most frequently occurring cancers in this population. Multi-center consortia may be the only way to identify and evaluate treatment outcomes among persons with AIDS and cancer, and to determine the most effective therapies. We demonstrated a significant fraction of mortality attributable to cancer, suggesting that successful cancer treatments would result in meaningful declines in deaths among persons with AIDS and cancer, and possibly in the AIDS population in general.

It is challenging to care for persons with HIV/AIDS. Oftentimes, persons present to the medical system late in their course of HIV disease, and with multiple medical problems. Intersecting epidemics of substance abuse, poverty, and homelessness make adherence to HIV therapies and other programs (e.g.:

drug and alcohol treatment, smoking cessation therapy) difficult.[19] Lack of health insurance and access to the health care system further marginalize people with HIV/AIDS.[20;21] Public health programs which take a systems approach to identify and retain HIV-positive persons into medical care should result in better outcomes with regards to HIV-disease and as well as HIV-related cancers.[22] As HIV is increasingly considered with chronic disease management paradigms, HIV programs should include primary cancer prevention strategies and cancer screening (were applicable) as part of routine care. Notably, successful HIV prevention would also have a profound impact on reducing the incidence or severity of the cancers we evaluated.

Table 2. Summary of major cancer prevention strategies to consider among persons with AIDS

Cancer type	Primary prevention	Screening
KS	HAART	None
NHL	HAART	None
Cervical cancer	HPV vaccination	Pap smear
Anal cancer	HPV vaccination (?)	Pap smear
Hodgkin lymphoma	None	None
Liver cancer	HBV vaccination HBV/HCV prevention and therapy Alcohol reduction	None
Lung cancer	Smoking cessation	None

Note: Where screening is recommended and/or has been demonstrated to be cost-effective

Additional research is needed to answer a number of outstanding questions with regards to HIV/AIDS and cancer. Most studies have taken an

ecologic approach to assess the impact of HAART on cancer risk, and lack detailed information on HAART regimens (e.g.: type of drug, dose, and duration). Such information could determine if any antiviral drug, by itself, in combination with other drugs, and/or with other cancer risk factors, increases cancer risk. In addition, the interactions between chemotherapeutic agents and HAART are not fully understood, and should be investigated so as to optimize therapy for both HIV and cancer. As persons with HIV/AIDS continue to live longer, the impact of the natural aging process on cancer risk also needs to be studied.

Both dissertation studies found increased risks of anal cancer. As routine HPV vaccination recommendations are continually expanded,[17] studies are needed to determine vaccine efficacy in the prevention of HPV-associated precancer of the anus, and to clarify the role and timing of immune suppression in the natural history of this cancer.[6] Studies are also needed to determine the impact of HPV vaccination on risk of HPV cancers at other sites (i.e.: head and neck cancers) among HIV-positive men and women.

We also noted a troubling increase in Hodgkin lymphoma risk which warrants further investigation. It is possible that HAART immune restoration influences the natural history of Epstein-Barr virus infection and the production of inflammatory cytokines which promote Hodgkin lymphoma.[12] Future longitudinal studies utilizing biospecimens with accompanying detailed patient-level information on HAART regimens may shed light on these complex relationships.

We noted an excess of liver cancer among persons with AIDS. For both HBV and HCV infection, coinfection with HIV results in a higher proportion of

chronic infections relative to those who are HIV negative, and a shorter time to cirrhosis.[23] While one recent study found evidence supporting the role of AIDS-mediated immune suppression in the development of HBV/HCV-related liver cancer,[24] additional population-based evaluations are needed to confirm this finding. The interaction of host genetics, alcohol use and the possible hepatotoxic effects of HAART also need to be studied to gain a complete understanding of the excess risk of liver cancer in this population.

Lung cancer is the most frequently occurring non-AIDS-defining cancer, and research examining the role if infections, inflammation and immune reconstitution in the natural history of lung carcinogenesis in the context of HIV/AIDS are needed.[5] Tobacco exposure is important in the development of lung cancer, and persons with HIV have a higher prevalence of smoking relative to the general population. However, this excess accounts for only part of the increased lung cancer risk among persons with HIV/AIDS.[25;26] HIV infection may have an independent biological effect or act synergistically with tobacco exposure, and research is needed to clarify these pathways. Further, health services research may identify strategies to identify and treat lung cancer in this population, as persons with HIV/AIDS present with late-stage lung cancer, relative to HIV-negative individuals.[27] Finally, studies of cancer risk among persons with AIDS also provide useful information for other immune suppressed groups such as transplant recipients, and insight on cancer etiology among those with functioning immune systems (i.e.: the general population).[28]

These dissertation studies used a number of epidemiologic and statistical methods to assess cancer risk among persons with AIDS relative to the general population and changes in cancer outcomes over time (incidence, cumulative incidence and cancer-attributable mortality). In the first study, the standardized incidence ratios (SIRs) in years 3-5 and 6-10 after AIDS, as well as the SIRs in years 3-10 after AIDS combined in the HAART era, all reflected consistent increased risks for a number of AIDS-defining and non-AIDS-defining cancers. When we compared results of the Poisson derived rate ratios and Cox derived hazard ratios (Appendix III), our findings with regards to increasing or decreasing risk relative to widespread HAART use were also consistent. Where any inconsistencies between the modeling strategies were apparent, we attributed them to data coding or small sample size. Our findings were consistent across studies and using different methods, further underscoring the robustness of our findings and importance of our conclusions.

In the second analysis, our conclusion of declining cumulative incidence of AIDS-defining cancers was consistent with declines found in the first analysis. As well, for non-AIDS-defining cancers, findings of increasing cumulative incidence at 5-years were consistent for anal and liver cancer as well as for Hodgkin lymphoma. For lung cancer, the first study found a decrease relative to widespread HAART use, while the 5-year cumulative incidence increased significantly among persons diagnosed with AIDS during 1996-2006. While the different inclusion and exclusion criteria of each study certainly played a role in this difference, we further speculate that competing mortality may also account

for the observed decline in the first study: when competing mortality was accounted for, we detected an increase in lung cancer cumulative incidence. Due to the large sample size and population-based nature of the HIV/AIDS Cancer Match Study, we believe these findings are generalizable to the U.S. AIDS population and contribute in a meaningful way to the understanding of changing cancer risk in this population.

In summary, the spectrum of cancer outcomes among persons with AIDS continues to evolve in the HAART era. Relative to the general population, persons with longstanding AIDS continue to be at increased risk for a number of AIDS-defining cancers (specifically, KS and NHL, and to a lesser extent, cervical cancer) and non-AIDS-defining cancers (specifically, cancer of the anus, liver, lung and Hodgkin lymphoma) and mortality attributable to non-AIDS-defining cancers appears to be increasing. Persons with HIV/AIDS represent a growing segment of the population at increased risk for cancer and continued monitoring is warranted to guide treatment and prevention programs.

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APPENDICES

APPENDIX I

DETAILS OF THE U.S. HIV/AIDS CANCER MATCH STUDY

Data source

Data from the U.S. HIV/AIDS Cancer Match Study (HACM) were used for analyses conducted as part of this dissertation. HIV/AIDS surveillance registries from 9 states (Colorado, Connecticut, Florida, Georgia, Illinois, Massachusetts, Michigan, New Jersey, and Texas) and 6 metropolitan areas (New York city, Los Angeles, San Diego, San Francisco, Seattle and Washington, D.C.) were matched to corresponding cancer surveillance registries using a probabilistic matching algorithm.[1] Records of persons with HIV/AIDS diagnosed between 1980 through 2008 were linked on demographic characteristics which were assigned a weight to represent their importance. These characteristics included name, social security number, gender, dates of birth and death and race/ethnicity. The match was conducted individually in each state or city and a National Cancer Institute (NCI) computer contractor concatenated the area-specific files together to form the national file, which was used for this dissertation research. Details on the matching process follow:

Using Integrity software (formerly called AutoMatch), multiple passes were made between the HIV/AIDS file and the cancer file. This approach skimmed off the most likely matches first, and then examined less likely matches by considering other combinations of identifying factors. Each pass found exact matches on one or more variables and then scored how likely the matches were

to be true matches. Staff from both HIV/AIDS and cancer registries reviewed potential matches from each pass and made the final choices as to which records were to be included as matches. This was done by evaluating all identifying fields for all potential matches, the "match score", and a distribution of these scores.

Subsequent to the match all observations were de-identified and assigned a random unique identifying number and this de-identified database and versions of it were the data for this dissertation. Investigators have no method of identifying persons whose information was used to form the database. A link does exist between the de-identified database at NCI and the HIV/AIDS and cancer registry data files and that information is stored in a secure manner at both the HIV/AIDS and cancer registry sites and is not accessible to anyone other than staff at the participating site (not to NCI investigators).

AIDS surveillance data

AIDS is a reportable condition in all 50 states, and the District of Columbia, and a uniform surveillance case definition and reporting mechanisms are currently in place. Reports of persons with HIV and/or AIDS are received at state health department from physicians, hospitals and laboratories. These reports are de-identified and sent to the Centers for Disease Control and Prevention (CDC).[2]

Initially surveillance for AIDS was passive, but as increasing resources became available and the importance of high-quality data became evident to

describe the epidemic, many areas implemented active surveillance. The surveillance case definition has been modified a number of times (in 1985, 1987, 1993, and most recently in 2000).[2-4] Revisions were made to increase sensitivity and specificity and to include a range of conditions which indicate AIDS. All cases of HIV infection using the current case definition (1993 or later) must be laboratory confirmed. The revised 1993 case definition resulted in a dramatic increase in AIDS cases reported to CDC immediately after its implementation, the impact of which has been previously described and should be kept in mind when interpreting temporal trends in incidence.[3;5;6]

The completeness, validity and timeliness of reports varies by geographic region and data quality has increased over time. With these caveats in mind, CDC estimates that national AIDS surveillance data are more than 85-90% complete.[2] A recent evaluation of data quality in Louisiana, Massachusetts and San Francisco, found completeness to be >90% and the median reporting delay was 4 months.[6] These sites with high quality data are included in the HACM. Data elements routinely collected include demographic characteristics, date of AIDS onset, under what criteria the case definition was met, vital status, and in some instances, date of initiation of antiretroviral therapy. The CDC also estimates that ascertainment of deaths to be >90% complete.[2] HIV/AIDS registries obtain vital status information via routine linkage to state mortality files, the Social Security Administration's Death Master File, and the National Death Index. Matching to mortality databases is conducted at the state-level, at various time intervals, to a) identify previously unrecognized cases of HIV/AIDS by

evaluating underlying cause of death as reported on death certificates (cases of HIV/AIDS are recognized by determine which deaths have an HIV-related underlying cause of death, then determining whether or not they are in the case surveillance registry) and b) to detect deaths among persons who may have migrated out of the HIV/AIDS registry catchment area;[7;8] both numbers are used to obtain to derive more accurate estimates of incidence and prevalence.

For AIDS cases included in the HACM, the AIDS onset date was recorded among persons with HIV as the date they met the 1993 CDC case definition. For cases occurring prior to 1993, the onset date was retrospectively classified by individual registry staff.

Cancer surveillance data

Population-based surveillance for incident cancers first began in the U.S. in 1973, with the establishment of the NCI-funded *Surveillance, Epidemiology and End Results* (SEER) program. This is a resource-intensive active surveillance system currently operating in 18 areas (comprised of states, cities and rural areas), covering 26% of the United States population.[9] In 1992, the CDC established the National Program of Cancer Registries (NPCR) and national cancer estimates are obtained through the aggregation of data from both systems.[10] Some states participate in both NPCR and SEER, while others use only one surveillance system. However, every U.S. state and territory participates in at least one of these surveillance activities, and provide data used to derive national estimates of cancer burden of disease.

Reports of incident cancer cases are received from hospitals, physicians, therapeutic radiation facilities, surgical centers, and pathology laboratories. Data elements routinely collected through surveillance include demographic characteristics, tumor histology, topography, tumor behavior (e.g.: *in situ* or invasive), vital status and stage of disease.[11]

The NCI SEER program, NPCR and The North American Association of Central Cancer Registries (NAACCR) provide guidelines to cancer registries regarding completeness, timeliness, de-duplication rates and other criteria. In general, cancer incidence data take up to 2 years to verify for a given diagnosis year due to reporting delays from healthcare providers and the myriad of tests needed to accurately classify a malignancy.[10]

Data quality has increased over time for cancer registries. In 2004, 14/15 of the cancer registries included in the HACM received a “Gold” certification from NAACR for data quality. Criteria for this certification included: >95% completeness, 100% passing data quality edits, <=3% of cases identified through death certificates only, all reports received within 23 months (timeliness), <=2% missing data on sex, age and county and <=3% missing data on race.[12]

For cancer registries to be included in the HACM, they needed to be >90% complete for the years in the study (1980-2006).

Registry	Year cancer registry coverage complete
Colorado	2007
Connecticut	2005
District of Columbia	2006
Florida	2002
Illinois	2004
Los Angeles	2002
Massachusetts	2002
Michigan	2003
New Jersey	2002
New York	2000
Georgia	2001
San Diego	2000
Seattle	2005
San Francisco	2001
Texas	2003

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APPENDIX II

SUPPLEMENTARY TABLE FOR MANUSCRIPT I

Sensitivity analysis of changes in cancer risk in the HAART era (1996-2006)

In this sensitivity analysis, person-years were discounted by a total of 20% over the study period (main analysis discounted person-years by 10%).

Cancer type	RR	95%CI
All cancer	**0.3**	**(0.3-0.4)**
AIDS-defining cancers		
Kaposi sarcoma	**0.2**	**(0.2-0.2)**
Non-Hodgkin lymphoma	**0.3**	**(0.2-0.3)**
Burkitt NHL	**0.6**	**(0.4-1.0)**
Diffuse large B-cell NHL	**0.3**	**(0.3-0.3)**
CNS NHL	**0.2**	**(0.1-0.2)**
Other NHL	**0.2**	**(0.2-0.3)**
Cervix	0.8	(0.5-1.2)
Non-AIDS-defining cancers		
Oral cavity/pharynx	1.0	(0.7-1.5)
Lip	0.6	(0.2-2.0)
Tongue	**2.9**	**(1.1-7.8)**
Esophagus	1.1	(0.5-2.0)
Stomach	1.1	(0.5-2.4)
Small intestine	1.0	(0.1-11)
Colon/rectum	1.0	(0.7-1.4)
Anus	**3.0**	**(2.1-4.1)**
Liver	2.0	(0.9-4.0)
Pancreas	2.3	(0.4-13)
Larynx	1.3	(0.8-2.3)
Lung/bronchus	**0.8**	**(0.6-1.0)**
Bones/joints	∞	-
Soft tissue	0.9	(0.3-2.4)
Melanoma of the skin	1.1	(0.5-2.4)
Breast	1.8	(1.0-3.2)
Uterus	1.4	(0.3-7.4)
Ovary	0.5	(0.2-1.6)
Vagina/vulva	1.8	(0.4-7.8)
Prostate	**1.6**	**(1.1-2.4)**
Testis	1.3	(0.6-2.8)
Penis	3.7	(0.5-29)
Bladder	1.2	(0.5-3.0)
Kidney	0.9	(0.4-2.2)
Brain	0.7	(0.3-2.0)
Thyroid	1.2	(0.5-3.0)
Hodgkin lymphoma	**2.0**	**(1.3-3.0)**
Nodular sclerosis HL	1.5	(0.8-2.9)
Mixed cellularity HL	**2.5**	**(1.2-5.1)**
Other HL	**2.0**	**(1.1-3.9)**
Myeloma	**0.5**	**(0.2-1.0)**

Lymphocytic leukemia	0.4	(0.1-1.4)
Myeloid/monocytic leukemia	0.8	(0.4-1.5)
Mesothelioma	0.2	(0.1-1.2)
Miscellaneous	0.8	(0.5-1.1)
Poorly specified	**0.2**	**(0.2-0.3)**
All non-AIDS cancers	**1.2**	**(1.1-1.3)**

Table notes
Data are for the combined period 3-10 years after AIDS onset. The rate ratio (RR) compares incidence between the pre-HAART era (1990-1995) to the HAART era (1996-2006), adjusted for attained age (15-34, 35-44, 45+ years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic), and gender/mode of HIV exposure (males who reported male-to-male sex alone or with injection drug use, all other males, and females). Bolded values are significant at $P<.05$.
Abbreviations: CI, confidence interval; CNS, central nervous system; HAART, highly active antiretroviral therapy; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; SIR, standardized incidence ratio.

APPENDIX III

ALTERNATE APPROACH

FOR EXAMINING THE EFFECT OF HAART ON CANCER RISK

Cohort data can be analyzed using Poisson regression (as we did in the first paper) or Cox regression. In this analysis, changes in cancer risk during the 3-10 years after AIDS between the pre-HAART and HAART calendar periods were assessed using hazard ratios (HRs) obtained from Cox regression models and were compared to the rate ratios (RRs) obtained from Poisson regression models that we present in manuscript 1.

The Poisson model is a generalized linear model which in our study evaluated the cancer rate as a function of a linear combination of predictor variables. The Poisson model has the following 3 assumptions: 1) independence of observations, 2) probability of the event in a short interval is proportional to the length of the interval and 3) probability two events in such a short interval is zero. Our data reasonably met these assumptions. For the first assumption, observations were independent since persons with AIDS contributed to either period (pre-HAART or HAART) based on their year of AIDS diagnosis. For the second assumption, it is understood that the risk of the event (cancer) increases with proportionally with time, although no formal testing of this assumption was conducted. For the third assumption, it is also understood that the outcome (cancer) is rare. The Poisson model assessed the log linear relationship

between the cancer rate and HAART, as specified by the log link function and took the following form: $\ln(\lambda) = \beta_0 + \beta_1 X_1 + ... + \beta_K X_K$

The time-to-event Cox model is semi-parametric to the extent that no distribution is assumed *a priori* regarding the form of the baseline hazard and the model has 2 main assumptions: 1) non-informative censoring and 2) the proportional hazards assumption (PHA). Non-informative censoring assumes that censoring is not related to the probability of an event occurring. This assumption holds true in the current analysis as persons were censored if they died or at month 120 (the end of observation) if they remained cancer-free. As to the PHA, this allows for the survivor functions for 2 arbitrary groups within the data to change over time, but that they change at the same rate; that is, their plotted values on the log scale will remain parallel over time or that the 'relative hazard' is constant (this assumption is also implied in Poisson regression although not implicitly stated). In our analyses, we evaluated the PHA with statistical and graphical techniques. The Cox model evaluated the hazard of cancer for an individual *i* at time *t* as a product of the baseline hazard $\lambda_0(t)$ and a linear function of *K* covariates. The main effect of HAART (β_1) was time-dependent; a time-dependent variable was also included to allow for persons whose cancer occurred in the 1980s: $h_i(t) = \lambda_0(t)\exp\{\beta_1 X_{i1}(t)...\beta_K X_{iK}\}$.

In the Cox models, time-to-event was measured in months since AIDS onset. The start of an individual's time at-risk was the later (maximum) of either month 25 after AIDS or when follow-up for cancer began at the cancer registry. The end of a subject's time at-risk was the first month of an event or censoring.

Subjects were censored at their month of death or month 120, whichever came first (follow-up stopped at month 120). Persons entered at different months after AIDS onset because cancer registry coverage began at differing times; to account for persons entering at different time, we used delayed entry methods. For each cancer, a Cox model evaluated whether or not a person developed cancer as the outcome. To estimate the impact of HAART on cancer risk between 1990-1995 (pre-HAART era) and 1996-2006 (HAART era), we introduced a time-dependent variable defined as 1 if the cancer occurred in the first month of current calendar year 1996 or later and 0 if it occurred during the pre-HAART era, the same as the Poisson models. The Cox models were adjusted for the same variables as the Poisson models: attained age at cancer diagnosis, race/ethnicity, and gender/mode of HIV exposure (referred to as model A). These HRs are directly comparable to the RRs derived from the Poisson models presented in manuscript 1.

The table below presents the comparison of cancer risk in the 3-10 years after AIDS for the pre-HAART era to the HAART era using the Poisson and Cox methods. For the most common cancers (i.e.: the major AIDS-defining cancers and the major non-AIDS-defining cancers [lung cancer and Hodgkin lymphoma]) the point estimates (HRs and RRs) were approximately the same (or the difference in point estimates was quantitatively and qualitatively miniscule). For cancers with a smaller number of events, there was greater variability between the HRs and RRs, although with few exceptions, conclusions as to increasing or

decreasing risk relative to HAART were the same regardless of the analysis method.

The few differences between the results from the two methods can be attributed to a small number of events (small sample size) and to the design of the databases used in the analyses. Specifically, for the differences between the HR and RR for cancer of the cervix, liver, uterus and penis, the difference is due to the coding of dates. In the Poisson models, year of AIDS onset (regardless of month) and date (month since AIDS) of cancer occurrence were used to classify cancer as occurring in the HAART era or otherwise. This method therefore involved some rounding, which provided a somewhat crude approximation of the effect of HAART. In the Cox models, which are time-to-event in nature, AIDS onset (including year and month) and month of cancer onset were used to classify cancer as occurring in the HAART era or otherwise, a more precise definition. We evaluated the impact of coding by looking at the dates of specific cases of cancer and their exposure status in both the Poisson and Cox databases and concluded the differences are due to this mechanism.

We assessed the PHA using formal tests. We ran a second set of models (model B) which calculated individual HRs for each year of follow-up after AIDS and assessed model fit with a likelihood-ratio test that had a chi-square distribution, with degrees of freedom equal to the difference in the number of parameters between the first (model A) and second models (model B). If the P-value was <0.001 (Bonferroni corrected P-value adjusted for 45 comparisons [0.05/45]), we determined that the PHA was violated. Based on the likelihood

ratio tests, the all cancer category and non-Hodgkin lymphoma violated the PHA. We also visually assessed changes in the HRs (obtained from model B) by plotting them as a function of year after AIDS (see plots). From a graphical standpoint, only the “all cancer” category suggested a strong or consistent linear trend. For those 2 cancers, we constructed an additional model (model C) which included an interaction term as HAART*YEAR and the P-value served as a trend test for linear interaction of the HRs and follow-up time. None of these terms were significant, suggesting the absence of any strong time interaction and further supporting the use of model A to assess changes in cancer risk between the pre-HAART and HAART periods.

The results of this analysis demonstrate the utility of using time-to-event methods to evaluate risk in a cohort study and also demonstrate the robustness of the findings presented earlier obtained from Poisson regression. Poisson and Cox regression models can be used interchangeably to answer the same research question when assumptions of the modeling strategy selected are met. Preference for one method versus the other has to do with validity of the modeling strategy selected. In the current study, Poisson regression was used since we first presented incidence rates of cancer per 100,000 person-years and Poisson models are the natural framework to evaluate changes in incidence rates using person-time. However, as demonstrated, the Cox models yield similar and consistent results and would have resulted in the same conclusions with regards to increases or decreases in cancer risk between the two time periods compared. If the goal of a given analytic strategy is to present and

interpret changes in incidence rates, Poisson regression is preferred. However, if the goal is not dependent upon the interpretation of actual rates, but rather risk, then Cox regression is generally preferred as the assumptions of Cox regression are considered less restrictive. Finally, there are data coding considerations with regards to the use of either method: counts and person-time are required for Poisson models and a binary outcome and time-to-failure for Cox models. One can easily switch between methods with minimal coding and data manipulation.

Poisson derived rate ratios and Cox derived hazard ratios to assess changes in cancer risk in the HAART era (1996-2006)

Cancer type	RR	95%CI	HR	95%CI	P[a]	P[b]
All cancer	**0.3**	**(0.3-0.4)**	**0.4**	**(0.4-0.4)**	<0.001	0.013
AIDS-defining cancers						
Kaposi sarcoma	**0.2**	**(0.2-0.2)**	**0.2**	**(0.3-0.3)**	0.06	
Non-Hodgkin lymphoma	**0.3**	**(0.2-0.3)**	**0.3**	**(0.3-0.4)**	<0.001	0.1
Burkitt NHL	**0.6**	**(0.4-1.0)**	**0.6**	**(0.4-1.0)**	0.7	
Diffuse large B-cell NHL	**0.3**	**(0.3-0.3)**	**0.4**	**(0.3-0.4)**	0.001	
CNS NHL	**0.2**	**(0.1-0.2)**	**0.2**	**(0.2-0.3)**	0.03	
Other NHL	**0.2**	**(0.2-0.3)**	**0.3**	**(0.3-0.3)**	0.002	
Cervix	0.8	(0.5-1.2)	1.2	(0.7-1.8)	0.2	
Non-AIDS-defining cancers						
Oral cavity/pharynx	1.0	(0.7-1.4)	0.9	(0.7-1.5)	0.6	
Lip	0.6	(0.2-2.0)	0.7	(0.2-2.1)	1.0	
Tongue	**2.9**	**(1.1-7.7)**	2.0	(0.7-5.7)	0.6	
Esophagus	0.9	(0.4-2.0)	1.1	(0.5-2.4)	0.3	
Stomach	1.0	(0.5-2.4)	1.2	(0.5-2.7)	0.8	
Small intestine	1.0	(0.1-11)	0.9	(0.1-7.8)	0.9	
Colon/rectum	1.0	(0.7-1.4)	1.1	(0.7-1.6)	0.03	
Anus	**2.9**	**(2.1-4.0)**	**3.3**	**(2.1-4.8)**	0.2	
Liver	1.9	(0.9-3.9)	**0.3**	**(0.1-0.6)**	0.2	
Pancreas	2.2	(0.4-13)	1.5	(0.5-4.4)	0.9	
Larynx	1.3	(0.8-2.3)	1.5	(0.8-2.6)	0.3	
Lung/bronchus	**0.8**	**(0.6-0.9)**	0.9	(0.8-1.1)	0.04	
Bones/joints	∞	(0.2-∞)	∞	-	-	
Soft tissue	0.9	(0.3-2.4)	1.0	(0.4-2.5)	0.9	
Melanoma of the skin	1.1	(0.5-2.3)	1.5	(0.8-2.8)	0.6	
Breast	1.8	(1.0-3.2)	**2.4**	**(1.1-5.6)**	0.1	
Uterus	1.4	(0.3-7.4)	∞	-	1.0	
Ovary	0.5	(0.2-1.6)	0.8	(0.2-3.0)	1.0	
Vagina/vulva	1.8	(0.4-7.7)	1.3	(0.3-5.6)	0.7	
Prostate	**1.6**	**(1.1-2.3)**	**2.0**	**(1.2-3.2)**	0.7	
Testis	1.3	(0.6-2.8)	1.4	(0.6-3.4)	0.7	
Penis	3.7	(0.5-29)	∞	-	-	
Bladder	1.2	(0.5-2.9)	1.6	(0.6-4.0)	0.2	
Kidney	0.9	(0.4-2.1)	0.9	(0.4-1.9)	0.2	
Brain	0.7	(0.3-1.9)	0.5	(0.2-1.1)	0.5	
Thyroid	1.2	(0.5-3.0)	1.0	(0.4-2.8)	0.6	
Hodgkin lymphoma	**2.0**	**(1.3-2.9)**	**2.0**	**(1.4-3.0)**	0.4	
Nodular sclerosis HL	1.5	(0.8-2.9)	1.7	(0.8-3.4)	0.4	
Mixed cellularity HL	**2.4**	**(1.2-5.1)**	**2.1**	**(1.0-4.2)**	0.6	
Other HL	**2.0**	**(1.1-3.8)**	**3.9**	**(2.1-7.5)**	0.5	
Myeloma	**0.5**	**(0.2-1.0)**	0.8	(0.3-1.8)	0.9	
Lymphocytic leukemia	0.4	(0.1-1.4)	1.0	(0.3-3.1)	0.6	
Myeloid/monocytic leukemia	0.8	(0.4-1.5)	1.1	(0.6-2.2)	0.2	
Mesothelioma	0.2	(0.1-1.1)	0.4	(0.1-4.5)	0.7	
Miscellaneous	0.8	(0.5-1.1)	0.9	(0.6-1.2)	0.03	
Poorly specified	**0.2**	**(0.2-0.3)**	**0.3**	**(0.2-0.4)**	0.08	
All non-AIDS cancers	**1.2**	**(1.0-1.3)**	**1.2**	**(1.1-1.5)**	0.2	

Table notes

Data are for the combined period 3-10 years after AIDS onset. The hazard ratio (HR) and rate ratio (RR) compare risk between the pre-HAART (1990-1995) and HAART era (1996-2006), adjusted for attained age (15-34, 35-44, 45+ years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic), and gender/mode of HIV exposure (males who reported male-to-male sex alone or with injection drug use, all other males, and females).

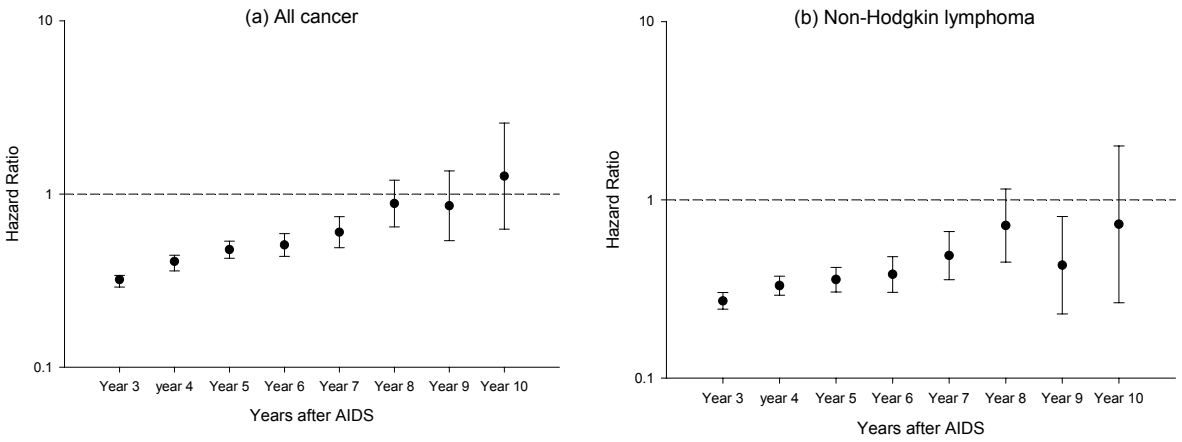
Bolded RR and HR values are significant at P<0.05.

P^a represents P-value obtained from the likelihood-ratio tests comparing model A to model B. When P<0.001, it was taken to indicate a potential change in the HRs over time.

P^b represents the P-value obtained for the linear interaction term of HAART*YEAR. When P<0.001, it was taken to indicate the presence of a significant interaction (that is the HRs changed significantly over time).

Abbreviations: CI, confidence interval; CNS, central nervous system; HAART, highly active antiretroviral therapy; HL, Hodgkin lymphoma; HR, hazard ratio; NHL, non-Hodgkin lymphoma.

Cox derived hazard ratios for the effect of HAART on selected cancer risk, during years 3-10 after AIDS onset



APPENDIX IV

SUPPLEMENTARY TABLES FOR MANUSCRIPT II

Sensitivity analysis of the impact of changes in demographic characteristics within the cohort on the cumulative incidence of death, AIDS-defining cancers, and non-AIDS-defining cancers

The cumulative incidence estimates in manuscript 2 accurately reflect changes in cancer risk within the overall cohort over time. However, we noticed changes in the demographic characteristics of the cohort across the calendar periods of AIDS onset; specifically with regards to gender, race/ethnicity and mode of HIV exposure since risk of some cancers varies with regards to these characteristics, we decided to perform a sensitivity analysis. As the cohort composition changed, it is possible that some of the changes observed in cancer cumulative incidence could be explained by these demographic changes. We conducted a stratified analysis to estimate cumulative incidence of ADC and NADC within these separate groups. Groups were defined as follows: gender/mode of HIV transmission (MSM, other males and females, 3 strata) and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other/unknown, 4 strata). Results were consistent with overall trends shown in Table 2 of manuscript 2, indicating that the overall trends in cumulative incidence were not due to demographic changes within the cohort. Stratified cumulative incidence estimates of each outcome are presented in the tables below. Were noteworthy differences in stratum-specific estimates were observed a comment is below the respective table.

Category	Cumulative incidence of death at five years of follow-up after AIDS onset					
	AIDS onset in 1980-1989		AIDS onset in 1990-1995		AIDS onset in 1996-2006	
	Cumulative Incidence	95% CI	Cumulative Incidence	95% CI	Cumulative Incidence	95% CI
Overall	75	74, 75	52	52, 53	19	19, 20
Gender/Mode of HIV transmission						
MSM	73	72, 74	49	48, 49	14	13, 14
Other Men	78	77, 80	57	57, 58	23	23, 24
Women	77	75, 80	55	54, 55	24	23, 24
Race/ethnicity						
Non-Hispanic white	73	73, 74	49	49, 50	14	14, 15
Non-Hispanic black	77	76, 77	57	56, 57	24	24, 25
Hispanic	76	75, 77	50	50, 51	15	15, 16
Other	68	63, 73	43	40, 45	13	11, 15

Within strata, MSM (who were mostly non-Hispanic white) and non-Hispanic white (who were mostly MSM) had consistently lower mortality relative to other groups. This is because non-Hispanic white MSM had increased access to care (early HIV therapies) which was associated with increased survival, relative to other groups. However, the trends within each sub-group of gender/mode of HIV transmission and race/ethnicity were in the same direction (trending downward over time) suggesting the overall trend we report is representative of trends in other groups of persons with AIDS.

Category	Cumulative incidence of AIDS-defining cancer at five years of follow-up after AIDS onset					
	AIDS onset in 1980-1989		AIDS onset in 1990-1995		AIDS onset in 1996-2006	
	Cumulative Incidence	95% CI	Cumulative Incidence	95% CI l	Cumulative Incidence	95% CI
Overall	8.7	8.5, 8.9	6.4	6.3, 6.5	2.1	2.0, 2.2
Gender/mode of HIV transmission						
MSM	13	12, 13	10	10, 10	2.9	2.7, 3.0
Other Men	2.5	2.2, 2.7	3.0	2.9, 3.2	1.7	1.5, 1.8
Women	2.3	1.9, 2.6	2.4	2.2, 2.6	1.5	1.3, 1.7
Race/ethnicity						
Non-Hispanic white	12	11, 13	9.0	8.8, 9.3	2.4	2.2, 2.6
Non-Hispanic black	3.7	3.4, 3.9	3.5	3.3, 3.6	1.8	1.7, 1.9
Hispanic	7.1	6.6, 7.6	6.8	6.5, 7.0	2.4	2.2, 2.6
Other	14	11, 17	9.6	8.3, 11	2.7	1.8, 3.7

Note that the predominant type of AIDS-defining cancer among those with AIDS onset during 1980-1989 and 1990-1995 was Kaposi sarcoma. Within strata, MSM (who were mostly non-Hispanic white) and non-Hispanic white (who were mostly MSM) had consistently higher cumulative incidence of AIDS-defining cancer, relative to other groups. This is because non-Hispanic white MSM experience focused outbreaks of Kaposi sarcoma throughout the course of the HIV/AIDS epidemic. However, the trends within each sub-group of gender/mode of HIV transmission and race/ethnicity were in the same direction (trending downward over time) suggesting the overall trend we report is representative of trends in other groups of persons with AIDS.

Category	Cumulative incidence of Kaposi sarcoma at five years of follow-up after AIDS onset					
	AIDS onset in 1980-1989		AIDS onset in 1990-1995		AIDS onset in 1996-2006	
	Cumulative Incidence	95% CI	Cumulative Incidence	95% CI	Cumulative Incidence	95% CI
Overall	6.3	6.1, 6.5	3.8	3.7, 3.9	0.89	0.84, 0.95
Gender/mode of HIV transmission						
MSM	9.5	9.2, 9.8	6.7	6.5, 6.8	1.5	1.4, 1.6
Other Men	1.2	1.0, 1.4	1.1	1.1, 1.3	0.6	0.5, 0.7
Women	0.9	0.6, 1.1	0.6	0.5, 0.7	0.3	0.2, 0.3
Race/ethnicity						
Non-Hispanic white	9.1	8.8, 9.5	5.5	5.4, 5.7	1.0	0.9, 1.1
Non-Hispanic black	2.5	2.3, 2.7	1.9	1.8, 2.0	0.8	0.7, 0.9
Hispanic	5.1	4.6, 5.5	3.9	3.7, 4.1	1.0	0.8, 1.1
Other	8.1	5.8, 10.4	7.0	5.8, 8.1	1.2	0.6, 1.8

With regards to Kaposi sarcoma, the cumulative incidence of this cancer predominated in men (MSM and non-Hispanic white males). However, among all persons diagnosed with AIDS across time and within all strata, we documented consistent declines in the 5-year cumulative incidence of Kaposi sarcoma.

Category	Cumulative incidence of non-Hodgkin lymphoma at five years of follow-up after AIDS onset					
	AIDS onset in 1980-1989		AIDS onset in 1990-1995		AIDS onset in 1996-2006	
	Cumulative Incidence	95% CI	Cumulative Incidence	95% CI	Cumulative Incidence	95% CI
Overall	2.3	2.2, 2.5	2.6	2.5, 2.6	1.2	1.1, 1.2
Gender/mode of HIV transmission						
MSM	3.0	2.8, 3.2	3.4	3.3, 3.5	1.4	1.2, 1.5
Other Men	1.3	1.1, 1.4	1.8	1.7, 1.9	1.1	1.0, 1.2
Women	1.2	1.0, 1.5	1.5	1.4, 1.7	0.9	0.8, 1.0
Race/ethnicity						
Non-Hispanic white	3.0	3.0, 3.4	3.5	3.4, 3.6	1.4	1.2, 1.5
Non-Hispanic black	1.1	1.0, 1.3	1.4	1.3, 1.5	0.9	0.8, 1.0
Hispanic	2.0	1.7, 2.2	2.8	2.7, 3.0	1.4	1.2, 1.5
Other	5.7	3.7, 7.7	2.7	2.0, 3.4	1.6	0.8, 2.4

Within strata of non-Hodgkin lymphoma, again in earlier AIDS onset calendar periods, we noted higher cumulative incidence among MSM and non-Hispanic whites. Although, the declines in non-Hodgkin lymphoma noted in the overall category were observed within every strata we analyzed.

Category	Cumulative incidence of cervical cancer at five years of follow-up after AIDS onset					
	AIDS onset in 1980-1989		AIDS onset in 1990-1995		AIDS onset in 1996-2006	
	Cumulative Incidence	95% CI	Cumulative Incidence	95% CI	Cumulative Incidence	95% CI
Overall	0.16	0.07, 0.26	0.28	0.23, 0.34	0.33	0.26, 0.40
Race/ethnicity						
Non-Hispanic white	0.15	0, 0.35	0.30	0.17, 0.43	0.36	0.18, 0.53
Non-Hispanic black	0.14	0.02, 0.26	0.32	0.24, 0.40	0.36	0.27, 0.45
Hispanic	0.25	0, 0.51	0.18	0.08, 0.28	0.23	0.09, 0.38
Other	0	-	0	-	0	-

Category	Cumulative incidence of non-AIDS-defining cancer at five years of follow-up after AIDS onset					
	AIDS onset in 1980-1989		AIDS onset in 1990-1995		AIDS onset in 1996-2006	
	Cumulative Incidence	95% CI	Cumulative Incidence	95% CI	Cumulative Incidence	95% CI
Overall	0.86	0.78, 0.93	1.1	1.0, 1.1	1.0	1.0, 1.1
Gender/mode of HIV transmission						
MSM	0.90	0.80, 1.0	1.0	0.95, 1.08	0.82	0.73, 0.91
Other Men	0.84	0.69, 0.99	1.24	1.15, 1.34	1.4	1.3, 1.5
Women	0.65	0.45, 0.84	0.94	0.84, 1.04	0.88	0.75, 1.0
Race/ethnicity						
Non-Hispanic white	0.97	0.85, 1.08	1.1	1.1, 1.2	1.1	0.93, 1.18
Non-Hispanic black	0.77	0.64, 0.90	1.2	1.1, 1.2	1.2	1.1, 1.3
Hispanic	0.70	0.53, 0.86	0.8	0.7, 0.9	0.65	0.54, 0.76
Other	0.79	0.05, 1.53	1.1	0.7, 1.6	0.94	0.27, 1.6

Category	Cumulative incidence of anal cancer at five years of follow-up after AIDS onset					
	AIDS onset in 1980-1989		AIDS onset in 1990-1995		AIDS onset in 1996-2006	
	Cumulative Incidence	95% CI	Cumulative Incidence	95% CI	Cumulative Incidence	95% CI
Overall	0.03	0.01, 0.04	0.08	0.07, 0.10	0.15	012, 0.20
Gender/mode of HIV transmission						
MSM	0.04	0.02, 0.06	0.13	0.10, 0.15	0.26	0.21, 0.32
Other Men	0.01	0, 0.02	0.04	0.03, 0.06	0.07	0.03, 0.10
Women	0	-	0.04	0.02, 0.06	0.06	0.02, 0.10
Race/ethnicity						
Non-Hispanic white	0.03	0.01, 0.05	0.12	0.09, 0.14	0.24	0.18, 0.30
Non-Hispanic black	0.01	0, 0.02	0.06	0.04, 0.08	0.10	0.07, 0.14
Hispanic	0.05	0, 0.09	0.06	0.03, 0.08	0.12	0.06, 0.17
Other	0.2	0, 0.6	0.16	0, 0.33	0.06	0, 0.18

Category	Cumulative incidence of Hodgkin lymphoma at five years of follow-up after AIDS onset					
	AIDS onset in 1980-1989		AIDS onset in 1990-1995		AIDS onset in 1996-2006	
	Cumulative Incidence	95% CI	Cumulative Incidence	95% CI	Cumulative Incidence	95% CI
Overall	0.04	0.02, 0.06	0.10	0.09, 0.12	0.17	0.15, 0.20
Gender/mode of HIV transmission						
MSM	0.04	0.02, 0.06	0.14	0.12, 0.17	0.22	0.17, 0.26
Other Men	0.05	0.02, 0.09	0.07	0.05, 0.09	0.19	0.14, 0.23
Women	0.02	0, 0.05	0.06	0.03, 0.08	0.08	0.05, 0.12
Race/ethnicity						
Non-Hispanic white	0.05	0.02, 0.07	0.13	0.10, 0.16	0.21	0.16, 0.26
Non-Hispanic black	0.02	0, 0.05	0.08	0.06, 0.11	0.14	0.10, 0.17
Hispanic	0.06	0.01, 0.10	0.09	0.06, 0.12	0.21	0.15, 0.28
Other	0	-	0.05	0-0.15	0.12	0, 0.28

Category	Cumulative incidence of liver cancer at five years of follow-up after AIDS onset					
	AIDS onset in 1980-1989		AIDS onset in 1990-1995		AIDS onset in 1996-2006	
	Cumulative Incidence	95% CI	Cumulative Incidence	95% CI	Cumulative Incidence	95% CI
Overall	0.01	0, 0.02	0.03	0.03, 0.04	0.08	0.06, 0.10
Gender/mode of HIV transmission						
MSM	0.01	0, 0.2	0.03	0.02, 0.04	0.09	0.06, 0.13
Other Men	0.02	0, 0.05	0.04	0.02, 0.06	0.10	0.06, 0.14
Women	0	-	0.03	0.01, 0.05	0.02	0, 0.04
Race/ethnicity						
Non-Hispanic white	0.01	0, 0.02	0.03	0.02, 0.05	0.09	0.05, 0.13
Non-Hispanic black	0.02	0, 0.04	0.03	0.02, 0.05	0.08	0.05, 0.11
Hispanic	0.01	0, 0.03	0.04	0.02, 0.06	0.06	0.02, 0.09
Other	0	-	0.05	0, 0.015	0.09	0, 0.25

Category	Cumulative incidence of lung cancer at five years of follow-up after AIDS onset					
	AIDS onset in 1980-1989		AIDS onset in 1990-1995		AIDS onset in 1996-2006	
	Cumulative Incidence	95% CI	Cumulative Incidence	95% CI	Cumulative Incidence	95% CI
Overall	0.14	0.11, 0.18	0.28	0.26, 0.31	0.37	0.33, 0.41
Gender/mode of HIV transmission						
MSM	0.11	0.08, 0.15	0.22	0.19, 0.25	0.27	0.22, 0.33
Other Men	0.25	0.17, 0.33	0.41	0.36, 0.47	0.55	0.46, 0.63
Women	0.08	0.01, 0.15	0.24	0.19, 0.29	0.28	0.21, 0.35
Race/ethnicity						
Non-Hispanic white	0.13	0.09, 0.18	0.27	0.24, 0.31	0.36	0.29, 0.43
Non-Hispanic black	0.22	0.15, 0.29	0.37	0.32, 0.41	0.45	0.39, 0.52
Hispanic	0.03	0, 0.07	0.15	0.11, 0.19	0.18	0.12, 0.24
Other	0	-	0.21	0.01, 0.41	0.24	0, 0.58

Notes:
Abbreviation: CI, confidence interval
Cumulative incidence was calculated using competing risk methods at 60-months of follow-up, expressed as a percentage (%) of people with the specified outcome.

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Education

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Training

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