

Cancer Burden in the HIV-Infected Population in the United States

Meredith S. Shiels, Ruth M. Pfeiffer, Mitchell H. Gail, H. Irene Hall, Jianmin Li, Anil K. Chaturvedi, Kishor Bhatia, Thomas S. Uldrick, Robert Yarchoan, James J. Goedert, Eric A. Engels

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Correspondence to: Meredith S. Shiels, PhD, MHS, Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd, EPS 7059, Rockville, MD 20852 (e-mail: shielsms@mail.nih.gov).

Background Effective antiretroviral therapy has reduced the risk of AIDS and dramatically prolonged the survival of HIV-infected people in the United States. Consequently, an increasing number of HIV-infected people are at risk of non-AIDS-defining cancers that typically occur at older ages. We estimated the annual number of cancers in the HIV-infected population, both with and without AIDS, in the United States.

Methods Incidence rates for individual cancer types were obtained from the HIV/AIDS Cancer Match Study by linking 15 HIV and cancer registries in the United States. Estimated counts of the US HIV-infected and AIDS populations were obtained from Centers for Disease Control and Prevention surveillance data. We obtained estimated counts of AIDS-defining (ie, Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer) and non-AIDS-defining cancers in the US AIDS population during 1991–2005 by multiplying cancer incidence rates and AIDS population counts, stratified by year, age, sex, race and ethnicity, transmission category, and AIDS-relative time. We tested trends in counts and standardized incidence rates using linear regression models. We multiplied overall cancer rates and HIV-only (HIV infected, without AIDS) population counts, available from 34 US states during 2004–2007, to estimate cancers in the HIV-only population. All statistical tests were two-sided.

Results The US AIDS population expanded fourfold from 1991 to 2005 (96 179 to 413 080) largely because of an increase in the number of people aged 40 years or older. During 1991–2005, an estimated 79 656 cancers occurred in the AIDS population. From 1991–1995 to 2001–2005, the estimated number of AIDS-defining cancers decreased by greater than threefold (34 587 to 10 325 cancers; $P_{\text{trend}} < .001$), whereas non-AIDS-defining cancers increased by approximately threefold (3193 to 10 059 cancers; $P_{\text{trend}} < .001$). From 1991–1995 to 2001–2005, estimated counts increased for anal (206 to 1564 cancers), liver (116 to 583 cancers), prostate (87 to 759 cancers), and lung cancers (875 to 1882 cancers), and Hodgkin lymphoma (426 to 897 cancers). In the HIV-only population in 34 US states, an estimated 2191 non-AIDS-defining cancers occurred during 2004–2007, including 454 lung, 166 breast, and 154 anal cancers.

Conclusions Over a 15-year period (1991–2005), increases in non-AIDS-defining cancers were mainly driven by growth and aging of the AIDS population. This growing burden requires targeted cancer prevention and treatment strategies.

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People with HIV infection and AIDS have an elevated cancer risk (1–9). Compared with the general population, HIV-infected individuals have a 3640-fold increased risk of Kaposi sarcoma (KS) caused by human herpesvirus 8 (HHV8), a 77-fold increased risk of non-Hodgkin lymphomas (NHL), some of which are caused by Epstein–Barr virus, and a sixfold increased risk of cervical cancer caused by oncogenic subtypes of human papillomavirus (HPV) (8). These malignancies are AIDS-defining cancers, based on the Centers for Disease Control and Prevention (CDC) definition of AIDS (11). HIV-infected people also have an increased risk of a number of non-AIDS-defining cancers (1–9), including some

associated with coinfections (eg, anal and oropharyngeal cancers associated with HPV infection, liver cancer associated with infection with hepatitis B and C viruses, and Hodgkin lymphoma associated with Epstein–Barr virus infection) or with cigarette smoking (eg, lung cancer) (5,6,8,10).

Among HIV-infected individuals, the availability of highly active antiretroviral therapy (HAART) since 1996 has improved immune function, reduced the risk of AIDS, and dramatically prolonged survival (12,13). Thus, KS and NHL incidence among HIV-infected individuals has declined markedly over time (1,4,14,15). In addition, increased longevity has resulted in a

CONTEXT AND CAVEATS

Prior knowledge

The HIV-infected population is at a higher risk of AIDS-defining cancers such as Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer. Since the advent of highly active antiretroviral therapy (HAART) in 1996, the survival of HIV-infected population in the United States has increased dramatically. The aging HIV-infected population, with or without AIDS, is at risk of non-AIDS-defining cancers (excluding AIDS-defining cancers) that usually occur at older ages.

Study design

Estimated counts of individual AIDS-defining and non-AIDS-defining cancers in the US AIDS and HIV-infected populations were obtained using data from the HIV/AIDS Cancer Match Study, which links 15 US population-based HIV and cancer registries, and from the Centers for Disease Control and Prevention. The study was divided into three calendar periods: 1991–1995 (pre-HAART), 1996–2000 (early-HAART), and 2001–2005 (late-HAART). Cancer counts in the HIV-only (HIV infected, without AIDS) population in 34 US states were also estimated (2004–2007).

Contribution

From 1991 to 2005, the US AIDS population increased by fourfold. This increase was primarily because of an increase in people aged 40 years or older. AIDS-defining cancers decreased by more than threefold, whereas non-AIDS-defining cancers increased by three fold during this period. In 34 US states, approximately 29% of non-AIDS-defining cancers occurred in the HIV-only population during 2004–2007.

Implications

A steep increase in the burden of non-AIDS-defining cancers in the aging HIV-infected population is noted, which is a serious public health issue. Effective strategies are needed to reduce this burden.

Limitations

Data were limited for the HIV-only population (available for 34 US states during 2004–2007), and cancer registry data for the AIDS population were also limited for the most recent calendar years, resulting in unstable estimated cancer counts.

From the Editors

growing HIV population that is aging. Approximately 28.4% of the 433 760 people living with AIDS in the United States in 2005 were aged 50 years or older (16). Furthermore, 15% of all new HIV diagnoses in 2005 occurred among people aged 50 years or older (17). Consequently, a growing number of HIV-infected people, with or without AIDS, are at risk of non-AIDS-defining cancers that typically occur at older ages.

Although trends in cancer incidence rates among HIV-infected individuals have been well studied in recent years (1–9), there are no published estimates on the number of cancers (ie, cancer burden) or types of cancer that occur each year among HIV-infected individuals in the United States. We hypothesized that the elevated cancer risk in the HIV-infected population, combined with growth and aging of this population, has led to an increase in the number of non-AIDS-defining cancers (18). An increase in the

cancer burden or a shift in distribution of cancer types among HIV-infected individuals in the United States would point to areas of emerging clinical and public health need. Therefore, in this study, we evaluated the trends in the cancer burden among people with AIDS in the United States during 1991–2005, using national AIDS prevalence data and representative cancer rates. We also estimated the cancer burden in HIV-infected people without AIDS (ie, HIV-only) during 2004–2007 using more limited recent data from 34 US states.

Subjects and Methods

Study Populations

Since 1982, AIDS diagnoses have been uniformly reported to the CDC by registries in all 50 US states and the District of Columbia (DC). In 1994, CDC additionally implemented data management for national reporting of HIV infection integrated with AIDS case reporting. For 2004–2007, HIV-only data were available from 34 US states that had reported HIV diagnoses for at least 4 years, a period sufficient to allow for stabilization of data collection. The states were Alabama, Alaska, Arizona, Arkansas, Colorado, Florida, Georgia, Idaho, Indiana, Iowa, Kansas, Louisiana, Michigan, Minnesota, Mississippi, Missouri, Nebraska, Nevada, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, South Carolina, South Dakota, Tennessee, Texas, Utah, Virginia, West Virginia, Wisconsin, and Wyoming. All new HIV and AIDS diagnoses are reported by the state health departments to the CDC. The CDC estimated the number of people living with AIDS (50 states and DC) from 1991 to 2005 and the number of people living with HIV-only (34 states) from 2004 to 2007, at the end of each calendar year, with statistical adjustments made for reporting delays and cases of HIV with missing risk factor information (19,20).

The ongoing HIV/AIDS Cancer Match (HACM) Study links 15 US population-based HIV and cancer registries (21). A probabilistic algorithm is used to match records based on name, social security number, sex, birth date, death date, and race. Only anonymized data are retained by investigators. As described previously (1), malignancies documented in cancer registries were categorized as AIDS-defining cancers (KS, NHL, and cervical cancer), non-AIDS-defining cancers (all cancers excluding KS, NHL, and cervical cancer), or poorly specified malignancies (ie, cancers with unspecified histology codes). All 15 HACM registries provided data on cancers occurring at or after AIDS diagnosis (423 855 people with AIDS during 1991–2005, which was 49% of the total US AIDS population). Five HACM registries (Colorado, Florida, New Jersey, Texas, and Michigan) also provided data on cancer incidence for people with HIV-only (92 298 people with HIV-only during 1998–2005) (1,2). The HACM Study was approved by the institutional review boards at the participating registries. More information about the HACM Study can be found at www.hivmatch.cancer.gov.

Statistical Analysis

Cancer incidence rates were estimated with data from the HACM Study by dividing the number of cancers by person-years of follow-up. The cancer burden for the US AIDS population was

estimated by multiplying cancer incidence rates in people with AIDS by CDC estimates of people with AIDS in strata defined by the following characteristics: calendar year (1991–2005), sex, current age (0–12, 13–19, 20–29, 30–39, 40–49, 50–59, and ≥ 60 years), race and ethnicity (white non-Hispanic, African American, Hispanic/Latino [Hispanic], and other), transmission category (men who have sex with men [MSM], injection drug users [IDU], MSM and IDU, heterosexual, and other), and time since AIDS (AIDS-relative time: 0–12, 13–24, 25–60, 61–120, and >120 months). For each cancer, we summed the counts across strata for each calendar year and for three calendar periods: January 1, 1991, to December 31, 1995 (pre-HAART period), January 1, 1996, to December 31, 2000 (early-HAART period), and January 1, 2001, to December 31, 2005 (late-HAART period). Cancer rates at 120 months or more after AIDS onset were increased by 10% to account for cancers that may not be ascertained by registries because of migration out of the registry area (22). In addition, we present yearly cancer rates standardized to the 2000 US AIDS population by age group, sex, and race to allow for the comparison of rates over time.

We also estimated the cancer burden separately for people with HIV-only and with AIDS in 34 US states. First, we estimated overall incidence rates in the HACM data from 1998 to 2007 for each cancer in people with HIV-only and in people with AIDS by dividing the total number of cancers by person-years of follow-up. Rates were multiplied by CDC estimates of the HIV-only and AIDS populations, respectively, in 34 states (2004–2007). The overall incidence rate for each cancer was used for the HIV-only and AIDS counts in this analysis because the data were too sparse to estimate rates in strata.

Poisson-based 95% confidence intervals (CIs) were estimated for cancer counts (23). For cancers in people with AIDS, we tested for a time trend in both counts and standardized rates. We fit linear regression models with the standardized rates or counts as the outcome and single calendar years as the independent variable. We incorporated the known variance of the counts and rates as weights in the model and obtained weighted least squares estimates of the coefficient for calendar year. We estimated the P value for trend using the χ^2 test. If the residuals from a model were found to violate normality, we instead used log-transformed counts or rates. All P values presented are two-sided, and all analyses were carried out using SAS version 9 (SAS, Cary, NC).

Results

Characteristics of AIDS and HIV-Only Populations and Estimates of Cancer Burden in the United States

Characteristics of AIDS and HIV-Only Populations. The number of people living with AIDS in the United States increased from 96 179 in 1991 to 413 080 in 2005, including a total of 3 955 556 person-years at risk of cancer (Figure 1, A). The characteristics of this AIDS population for three calendar periods (January 1, 1991, to December 31, 1995 [pre-HAART period], January 1, 1996, to December 31, 2000 [early-HAART period], and January 1, 2001, to December 31, 2005 [late-HAART period]) are shown in Table 1. The proportion of person-years contributed by people with AIDS younger than 30 years decreased from 15.1% in 1991–1995 to 5.9% in 2001–2005, whereas the proportion of person-years

contributed by people with AIDS aged 50 years or older increased from 9.8% to 24.8%. Thus, a substantial age shift in the AIDS population was noted, and the increase in size of the AIDS population was largely because of an increase in the number of people aged 40 years or older (Figure 1, A).

Compared with 1991–1995, people living with AIDS in 2001–2005 were less likely to be men, and more likely to be African American, Hispanic, or of other race and ethnicity (Table 1). The proportion of the AIDS population infected with HIV through heterosexual contact increased, although MSM continued to represent the largest HIV transmission risk group. There was also an increase in the number of person-years contributed by people who had AIDS for 120 months or more in 2001–2005 compared with 1991–1995.

In 34 US states during 2004–2007, people with HIV-only contributed a total of 946 936 person-years at risk of cancer, whereas people with AIDS contributed 1 101 658 person-years. People with HIV-only were younger than people with AIDS and were more likely to be women but had similar distributions of race and ethnicity and HIV transmission categories (Table 1).

Cancer Burden in the AIDS Population. During 1991–2005, an estimated 79 657 cancers (95% CI = 78 588 to 80 726 cancers) occurred in the US AIDS population (incidence rate = 2013 per 100 000 person-years). The most common cancers were KS (estimated number [n] = 31 037 cancers, 95% CI = 30 462 to 31 612 cancers) and NHL (n = 26 038 cancers, 95% CI = 25 440 to 26 636 cancers). Additional common cancers included lung cancer (n = 4140 cancers, 95% CI = 3865 to 4414 cancers), anal cancer (n = 2540 cancers, 95% CI = 2291 to 2789 cancers), Hodgkin lymphoma (n = 2004 cancers, 95% CI = 1811 to 2198 cancers), and cervical cancer (n = 1276 cancers, 95% CI = 1125 to 1427 cancers).

Figure 1 further depicts the trends in cancer burden in the AIDS population. From 1991 to 2005, AIDS-defining cancers declined in most age groups, with the largest declines among 20–39 year olds (Figure 1, B). The decline in cancer burden of AIDS-defining cancers was driven by a steep decline in the standardized incidence rate of these cancers ($P_{\text{trend}} < .001$) (Figure 1, B). In contrast, there was an increase in the cancer burden attributable to non-AIDS-defining cancers, which was limited to people aged 40 years or older (Figure 1, C). This rise in cancer burden occurred despite a modest decline in the standardized incidence rate ($P_{\text{trend}} < .001$) (Figure 1, C). As a result of these changes, the total cancer burden in the AIDS population decreased during 1991–1998, but increased subsequently, driven by the rise in number of non-AIDS-defining cancers (Figure 1, D).

Further details of the estimated cancer burden in the US AIDS population during three calendar periods (1991–1995, 1996–2000, and 2001–2005) are presented in Table 2; 95% confidence intervals for these estimated counts are presented in Supplementary Table 1 (available online). The number of AIDS-defining cancers declined and the number of non-AIDS-defining cancers increased across the three calendar periods ($P_{\text{trend}} < .001$ for both). During 1991–1995, only 8.2% of cancers were non-AIDS-defining cancers, but in 2001–2005, approximately equal numbers of AIDS-defining (49.6%) and non-AIDS-defining (48.3%) cancers occurred among people with AIDS. Poorly specified malignancies declined from 1142 during 1991–1995 to 438 during 2001–2005.

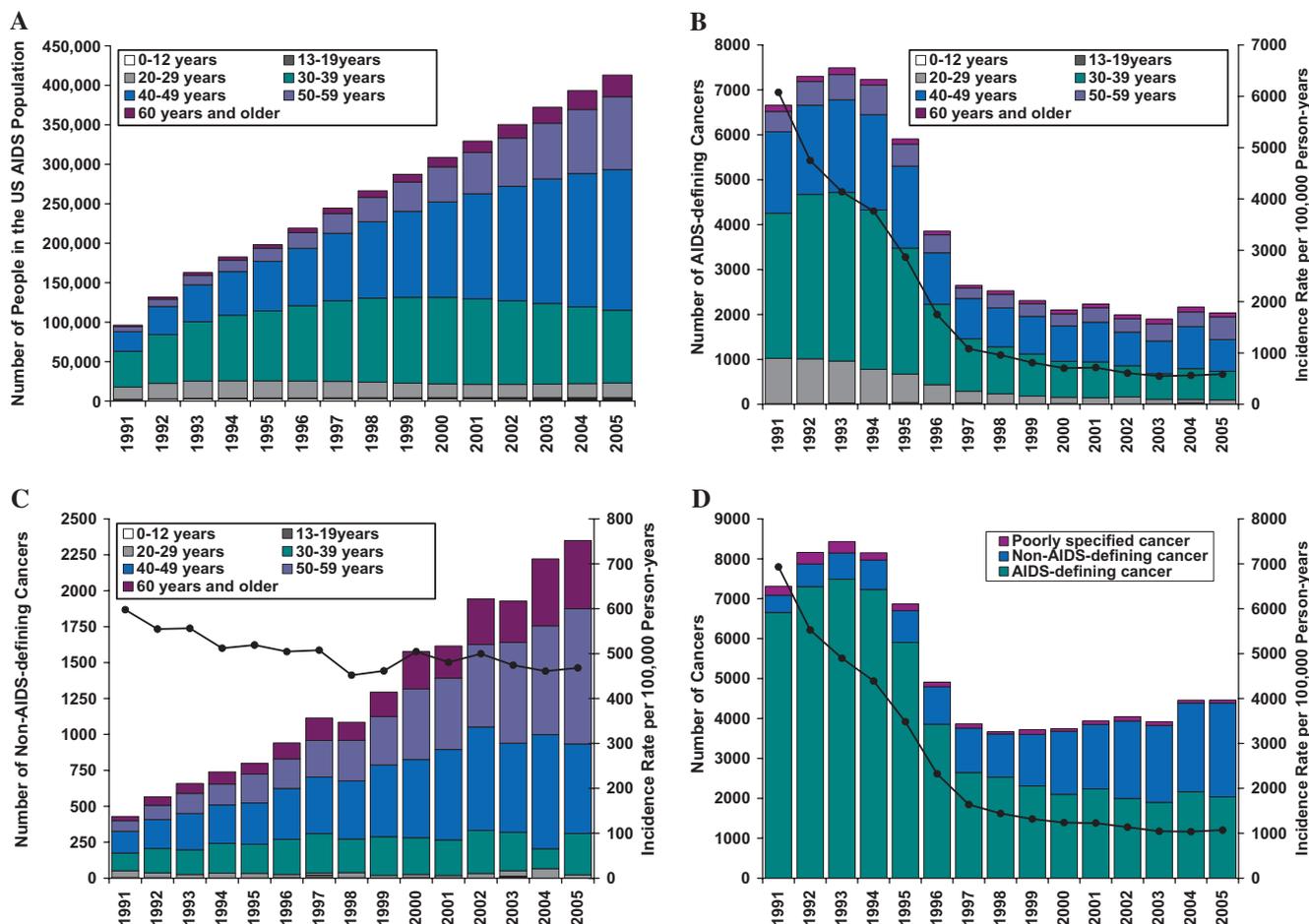


Figure 1. Number of people living with AIDS, AIDS-defining cancers, non-AIDS-defining cancers, and all cancers in the United States during 1991–2005. **A)** US AIDS population by calendar year and age group. **B)** The estimated counts and standardized rates of AIDS-defining cancers among people living with AIDS in the United States by calendar year and age group. **C)** The estimated counts and standardized rates of non-AIDS-defining cancers among people living with AIDS in the United States by calendar year and age group. Of note, the bars for 0–12 year olds in

panels **(B)** and **(C)** are difficult to see because of small numbers of cancers in this age group during 1991–2005 (122 AIDS-defining cancers and 25 non-AIDS-defining cancers). **D)** The estimated counts and standardized incidence rates of total cancers among people living with AIDS in the United States, stratified by AIDS-defining cancers, non-AIDS-defining cancers, and poorly specified cancers. **Bars** depict the estimated number of cancers, and **points connected by lines** depict incidence rates standardized to the 2000 US AIDS population by age group, race, and sex.

During 1991–2005, there was an approximately 82% decrease in KS (21 483 cancers in 1991–1995 to 3827 cancers in 2001–2005, $P_{\text{trend}} < .001$) and a 53% decrease in NHL (12 778 cancers in 1991–1995 to 5968 cancers in 2001–2005, $P_{\text{trend}} < .001$) (Table 2). These declines were explained by a sharp decline in incidence rates during 1991–1997, and a gradual decline thereafter (Figure 2, A and B). Eighty-nine percent of KS cases occurred in MSM; the number of KS cases declined in this group from 4175 in 1991 to 731 in 2005. A statistically significant increase in the number of cervical cancers was observed in women with AIDS from 1991–1995 to 2001–2005 (327 to 530 cancers; $P_{\text{trend}} < .001$), despite a declining incidence rate (Figure 2, C).

During 1991–2005, 19 263 non-AIDS-defining cancers occurred in the US AIDS population (Table 2). Statistically significant ($P_{\text{trend}} < .05$) increases in the number of most non-AIDS-defining cancers were noted during this time period. During 2001–2005, compared with 1991–1995, the largest absolute increases were observed for anal cancer (an increase of 1358 cancers), lung cancer (an increase of 1007 cancers), prostate cancer (an increase of 672

cancers), Hodgkin lymphoma (an increase of 471 cancers), and liver cancer (an increase of 467 cancers).

Approximately 50% of the estimated non-AIDS-defining cancers ($n = 9645$) were cases of lung cancer, anal cancer, liver cancer, and Hodgkin lymphoma. The annual counts and standardized incidence rates for these four cancers, which are known to occur more frequently among people with HIV (2,8,10), as well as for prostate and colorectal cancers, which are common but not clearly associated with HIV, are shown in Figure 3. For each of these cancers, a statistically significant increase in the number of cancers was observed over time (all $P_{\text{trend}} < .001$). An increase in the number of cancers was noted for lung cancer (Figure 3, B), liver cancer (Figure 3, C), Hodgkin lymphoma (Figure 3, D), and colorectal cancer (Figure 3, F), despite constant or decreasing standardized incidence rates. For anal cancer (Figure 3, A) and prostate cancer (Figure 3, E), increasing incidence rates over time contributed to the increasing number of cancers. The annual counts and standardized incidence rates for 26 other malignancies are presented in Supplementary Figure 1 (available online).

Table 1. Characteristics of people living with AIDS and HIV-only in the United States*

Characteristic	Persons-years contributed by the AIDS population in 50 US states and DC			Persons-years contributed by the HIV-infected population in 34 US states† by AIDS status	
	1991–1995, No. (%)	1996–2000, No. (%)	2001–2005, No. (%)	AIDS 2004–2007, No. (%)	HIV-only 2004–2007, No. (%)
	Person-years	771 517 (100)	1 326 055 (100)	1 857 984 (100)	1 101 658 (100)
Age, y					
0–12	12 978 (1.7)	14 892 (1.1)	10 117 (0.5)	3508 (0.3)	9908 (1.0)
13–19	3462 (0.4)	6326 (0.5)	12 267 (0.7)	8980 (0.8)	14 407 (1.5)
20–29	100 468 (13.0)	97 832 (7.4)	86 854 (4.7)	53 246 (4.8)	131 400 (13.9)
30–39	354 312 (45.9)	521 913 (39.4)	505 784 (27.2)	240 242 (21.8)	270 667 (28.6)
40–49	224 935 (29.2)	484 820 (36.6)	782 643 (42.1)	463 913 (42.1)	331 903 (35.1)
50–59	58 361 (7.6)	157 485 (11.9)	357 696 (19.3)	252 662 (22.9)	146 199 (15.4)
>60	17 001 (2.2)	42 787 (3.2)	102 623 (5.5)	79 107 (7.2)	42 452 (4.5)
Sex					
Men	643 378 (83.4)	1 051 262 (79.3)	1 438 847 (77.4)	824 956 (74.9)	662 432 (70.0)
Women	128 139 (16.6)	274 793 (20.7)	419 137 (22.6)	276 702 (25.1)	284 504 (30.0)
Race and ethnicity					
White non-Hispanic	359 564 (46.6)	526 248 (39.7)	676 451 (36.4)	360 852 (32.8)	316 452 (33.4)
African American	279 641 (36.2)	543 171 (41.0)	798 737 (43.0)	522 272 (47.4)	468 624 (49.5)
Hispanic	120 788 (15.7)	232 124 (17.5)	341 490 (18.4)	199 464 (18.1)	142 234 (15.0)
Other	11 524 (1.5)	24 512 (1.8)	41 306 (2.2)	19 070 (1.7)	19 626 (2.1)
HIV risk group					
MSM	384 563 (49.8)	604 881 (45.6)	850 448 (45.8)	484 711 (44.0)	431 485 (45.6)
IDU	209 812 (27.2)	360 796 (27.2)	444 427 (23.9)	244 308 (22.2)	158 039 (16.7)
MSM and IDU	69 453 (9.0)	106 740 (8.0)	130 218 (7.0)	66 843 (6.1)	43 002 (4.5)
Heterosexual	77 684 (10.1)	214 963 (16.2)	387 689 (20.9)	279 090 (25.3)	281 944 (29.8)
Children and adolescents	16 440 (2.1)	21 218 (1.6)	22 384 (1.2)	12 488 (1.1)	24 315 (2.6)
Other	13 565 (1.8)	17 457 (1.3)	22 818 (1.2)	14 218 (1.3)	8151 (0.9)
Months since AIDS diagnosis					
0–12	286 185 (37.1)	201 156 (15.2)	173 879 (9.4)	91 348 (8.3)	
13–24	197 984 (25.7)	203 391 (15.3)	166 059 (8.9)	88 378 (8.0)	
25–60	229 641 (29.8)	544 364 (41.1)	464 127 (25.0)	247 274 (22.4)	
61–120	55 017 (7.1)	334 407 (25.2)	743 153 (40.0)	370 039 (33.6)	
>120	2690 (0.3)	42 737 (3.2)	310 766 (16.7)	304 619 (27.7)	

* Centers for Disease Control and Prevention (CDC) surveillance data for the US AIDS population (1991–2005) and the AIDS and HIV-only populations (2004–2007) in 34 US states. The HIV-only population includes people with HIV infection but not AIDS. AIDS data are presented in three time periods: pre-highly active anti-retroviral therapy (HAART) period (1991–1995), early-HAART period (1996–2000) and late-HAART period (2001–2005). DC = District of Columbia; IDU = injection drug user; MSM = men who have sex with men.

† Thirty four states with CDC surveillance data for the HIV-only population: Alabama, Alaska, Arizona, Arkansas, Colorado, Florida, Georgia, Idaho, Indiana, Iowa, Kansas, Louisiana, Michigan, Minnesota, Mississippi, Missouri, Nebraska, Nevada, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, South Carolina, South Dakota, Tennessee, Texas, Utah, Virginia, West Virginia, Wisconsin and Wyoming.

The number of lung cancers in people with AIDS younger than 50 years remained relatively stable over time, whereas in people older than 50 years, the estimated number of lung cancers increased from 35 in 1991 to 283 in 2005. Additionally, prostate cancer occurred almost entirely (89%) in men older than 50 years across all calendar years. Eighty-three percent of all anal cancer occurred in MSM, with an increase in the estimated number among MSM from 18 in 1991 to 299 in 2005. Fifty-one percent of liver cancers occurred in IDUs, among whom the estimated number increased from 10 in 1991 to 78 in 2004. Of note, the number of cancers of the vulva, breast, and uterine corpus increased over time among women.

Cancer Burden in the HIV-Infected Population in 34 US States

During 2004–2007, an estimated total of 15 884 cancers occurred among HIV-infected people in 34 US states (Table 2), of which

7869 (49.5%) were AIDS-defining cancers and 7563 (47.6%) were non-AIDS-defining cancers. Of the non-AIDS-defining cancers, 2191 (29.0%) occurred in the HIV-only population. Among people with HIV-only, lung cancer comprised 19.7% of the cancer burden (n = 454 cancers). Other common cancers in people with HIV-only included female breast cancer (n = 166 cancers), anal cancer (n = 154 cancers), Hodgkin lymphoma (n = 150 cancers), and prostate cancer (n = 147 cancers); 95% confidence intervals for these estimated counts are presented in Supplementary Table 2 (available online).

Discussion

In this study, we demonstrated that the number of cancers (ie, cancer burden) and types of cancers among HIV-infected people in the United States changed dramatically during 1991–2005.

Table 2. Cancer burden in the HIV-infected population in the United States*

Cancer	Estimated number of cancers in people living with AIDS in 50 US states and DC			<i>P</i> _{trend} †	Estimated number of cancers in people in 34 US states living with AIDS or HIV-only	
	1991–1995	1996–2000	2001–2005		AIDS	HIV-only
					2004–2007	2004–2007
AIDS-defining cancers						
Kaposi sarcoma	21 483	5727	3827	<.001	2941	—
Non-Hodgkin lymphoma	12 778	7292	5968	<.001	4584	—
Cervix	327	419	530	.003	383	—
All AIDS-defining cancers	34 587	13 439	10 325	<.001	7869	—
Non-AIDS-defining cancers						
Oral cavity and pharynx	181	341	503	<.001	297	103
Esophagus	41	62	254	.002	86	25
Stomach	50	78	118	.06	67	41
Small intestine	13	25	24	.48	12	13
Colorectum	108	230	438	<.001	237	135
Anus	206	770	1,564	<.001	751	154
Liver	116	261	583	<.001	269	91
Pancreas	25	62	188	<.001	76	63
Larynx	70	192	317	<.001	161	50
Lung	875	1383	1882	<.001	1143	454
Bone	5	9	2	.15	2	9
Soft tissue including heart	33	43	112	.06	40	6
Melanoma	76	154	264	.001	120	25
Female breast	36	198	337	<.001	203	166
Uterine corpus	7	15	47	.04	19	20
Ovary	10	21	28	.10	31	20
Vagina	0	0	9	.10	4	0
Vulva	10	23	74	.01	39	17
Prostate	87	322	759	<.001	271	147
Testis	88	73	81	.95	38	22
Penis	13	35	64	.06	23	4
Bladder	31	62	70	.07	50	19
Kidney	66	97	208	<.001	104	75
Brain	44	53	61	.48	45	9
Thyroid	20	51	84	.02	47	34
Hodgkin lymphoma	426	682	897	<.001	546	150
Myeloma	63	93	159	.02	71	41
Lymphocytic leukemia	36	44	36	.88	29	13
Myeloid and monocytic leukemia	47	101	118	.06	67	25
Mesothelioma	12	9	14	.80	6	0
Miscellaneous	396	511	760	<.001	431	160
All non-AIDS-defining cancers	3193	6011	10 059	<.001	5372	2191
Poorly specified malignancy	1142	464	438	<.001	340	113
Total cancers	38 922	19 913	20 821	<.001	13 581	2303

* Estimated total number of cancers (ie, the cancer burden) occurring in the US AIDS population during the pre-highly active antiretroviral therapy (HAART) period (1991–1995), early-HAART period (1996–2000) and late-HAART period (2001–2005), and the estimated cancer burden in people with AIDS and HIV-only (HIV infected, without AIDS) in 34 US states during 2004–2007. Estimates were calculated by multiplying cancer incidence rates from the HIV/AIDS Cancer Match Study by US AIDS and HIV-only counts from Centers for Disease Control and Prevention HIV/AIDS surveillance data. DC = District of Columbia. Linear regression was used to estimate trends in cancer counts and rates.

† *P*_{trend} was calculated with across single calendar years from 1991 to 2005 among people with AIDS using a two-sided χ^2 test.

In the AIDS population, the number of AIDS-defining cancers declined sharply between 1991 and 1997 with more gradual decreases in subsequent years. Concurrently, the number of non-AIDS-defining cancers increased steadily from 1991 to 2005 and since 2003, has exceeded the annual number of AIDS-defining cancers. Consequently, we noted that the total cancer burden in people with AIDS has increased since 1998.

Several factors contributed to the dramatic increase in the estimated number of non-AIDS-defining cancers. Most noticeably, the

size of the AIDS population in the United States increased fourfold from 1991–1995 to 2001–2005, resulting in a substantial growth of the number of people at risk of cancer. Additionally, the cancer burden is compounded by the rising proportion of people with AIDS aged older than 40 years, as the incidence of most cancers increases with age. Finally, although the overall incidence rate for non-AIDS-defining cancers decreased over time, we observed increased incidence rates for some of these cancers, which, when applied to the population at risk, magnified the estimated number of incident cancers.

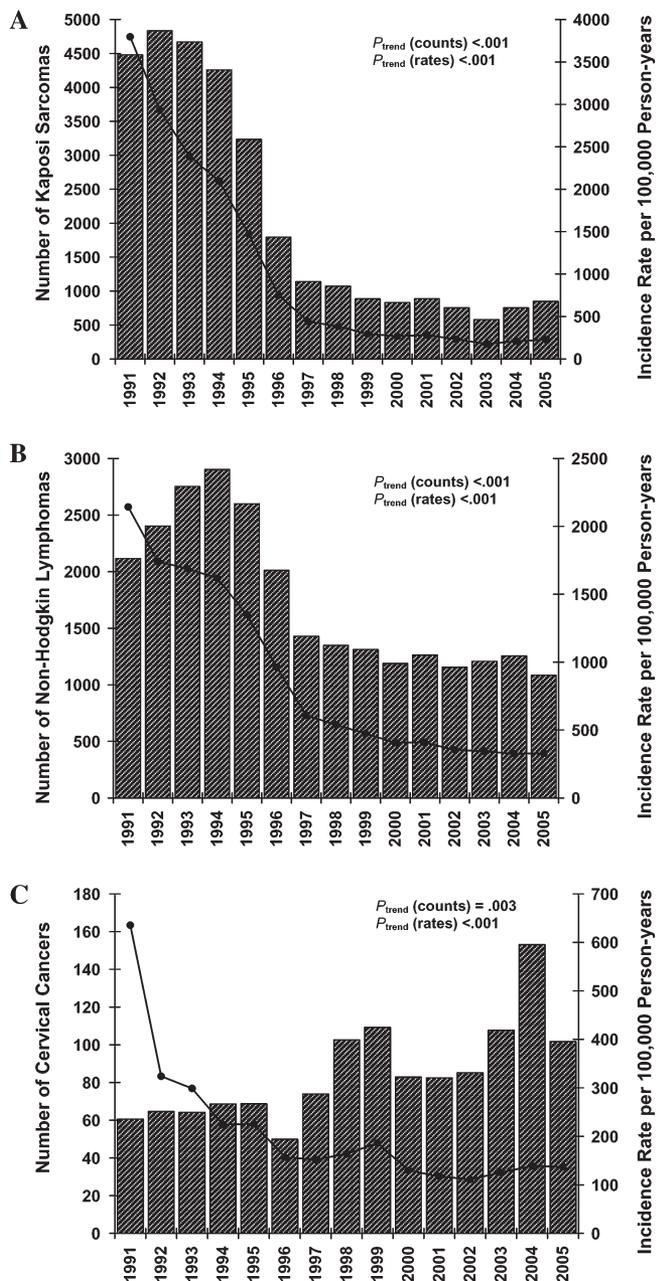


Figure 2. Cancer burden of Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer among people living with AIDS in the United States during 1991–2005. **A)** Estimated counts (ie, number of cancers) and standardized incidence rates of Kaposi sarcoma. **B)** Estimated counts and standardized incidence rates of non-Hodgkin lymphoma. **C)** Estimated counts and standardized incidence rates of cervical cancer among women. **Bars** depict the estimated counts and **points connected by lines** depict the incidence rates standardized to the 2000 US AIDS population by age group, race, and sex. Trends in cancer counts and rates were estimated with linear regression. Two-sided P values were calculated using the χ^2 test.

The precipitous drop in the number of cases of KS and NHL, despite the increase in the size of the AIDS population in the United States, is likely multifactorial. KS and NHL incidence began to decrease in the early 1990s, possibly because of the use of early combination antiretroviral therapy regimens or, for KS, changes in HHV8 epidemiology (1,2,4,25). Incidence declined further in 1996 with the introduction of HAART (1,4,14,15).

Despite these declines, NHL and KS remain the most common cancers in the AIDS population in the United States, with NHL now more common than KS. Furthermore, for people with AIDS in the United States, the risk of both malignancies has remained elevated during the HAART era compared with the general population (relative risks of 22.6 for NHL and 36.40 for KS) (1).

HIV-infected people are at an increased risk of many non-AIDS-defining cancers compared with the general population (1,5–7,9,10). In particular, the incidence rates of lung cancer, anal cancer, liver cancer, and Hodgkin lymphoma (1,2,4,10) are increased. In a meta-analysis (8), these risks were estimated to be increased threefold for lung cancer, 29-fold for anal cancer, fivefold for liver cancer, and 11-fold for Hodgkin lymphoma. Anal cancer, liver cancer, and Hodgkin lymphoma are each associated with coinfections (ie, HPV for anal cancer, hepatitis B and C viruses for liver cancer, and Epstein–Barr virus for Hodgkin lymphoma). The risks of these cancers in HIV-infected individuals are increased because of a greater prevalence of infection (for HPV and the hepatitis viruses) and an inability to control these infections with a suppressed immune system (5). Cigarette smoking is also far more common in HIV-infected individuals than the general population (26), contributing to increased rates of lung cancer. Furthermore, increased risk of lung cancer in HIV-infected individuals may be associated with frequent pulmonary infections, chronic inflammation, or nutrient deficiencies (27).

In the United States, during 1991–2005, lung cancer, anal cancer, liver cancer, and Hodgkin lymphoma comprised 50% of all non-AIDS-defining cancers in the AIDS population compared with only 16% of cancers in the general population (28). The cancer burden attributed to each of these four malignancies increased over time. The increase in number of lung cancers was restricted to people aged 50 years or older and was likely driven by the growth of the older AIDS population. Of these four cancers, the largest increase was seen for anal cancer (a greater than sevenfold increase from 1991–1995 to 2001–2005), where cancer was predominantly concentrated among MSM. We also observed an increase in the standardized incidence rate of anal cancer during 1991–2005, paralleling an increase in the rates of anal cancer observed in the general US population (29). Previous studies, including our own, have produced conflicting data on whether Hodgkin lymphoma incidence is increasing in HIV-infected people (2,4,30,31). In the present analysis, which included a longer follow-up, Hodgkin lymphoma incidence was stable, but the number of Hodgkin lymphomas increased nonetheless.

Although the number of prostate and colorectal cancers increased over time in people with AIDS, HIV-infected people do not have an increased risk of these cancers compared with the general population (1,2,4,10,32). When compared with the general population, risk in HIV-infected people is decreased by 30% for prostate cancer and by 8% for colorectal cancer (8). Most cases of prostate cancer were among people aged 50 years or older, suggesting that the growth of the AIDS population in this age group was responsible for the increase in the number of these cancers. Furthermore, in contrast to the decline in the incidence rates of prostate cancer observed in recent years among men in the general US population (33), we observed a statistically significant increase

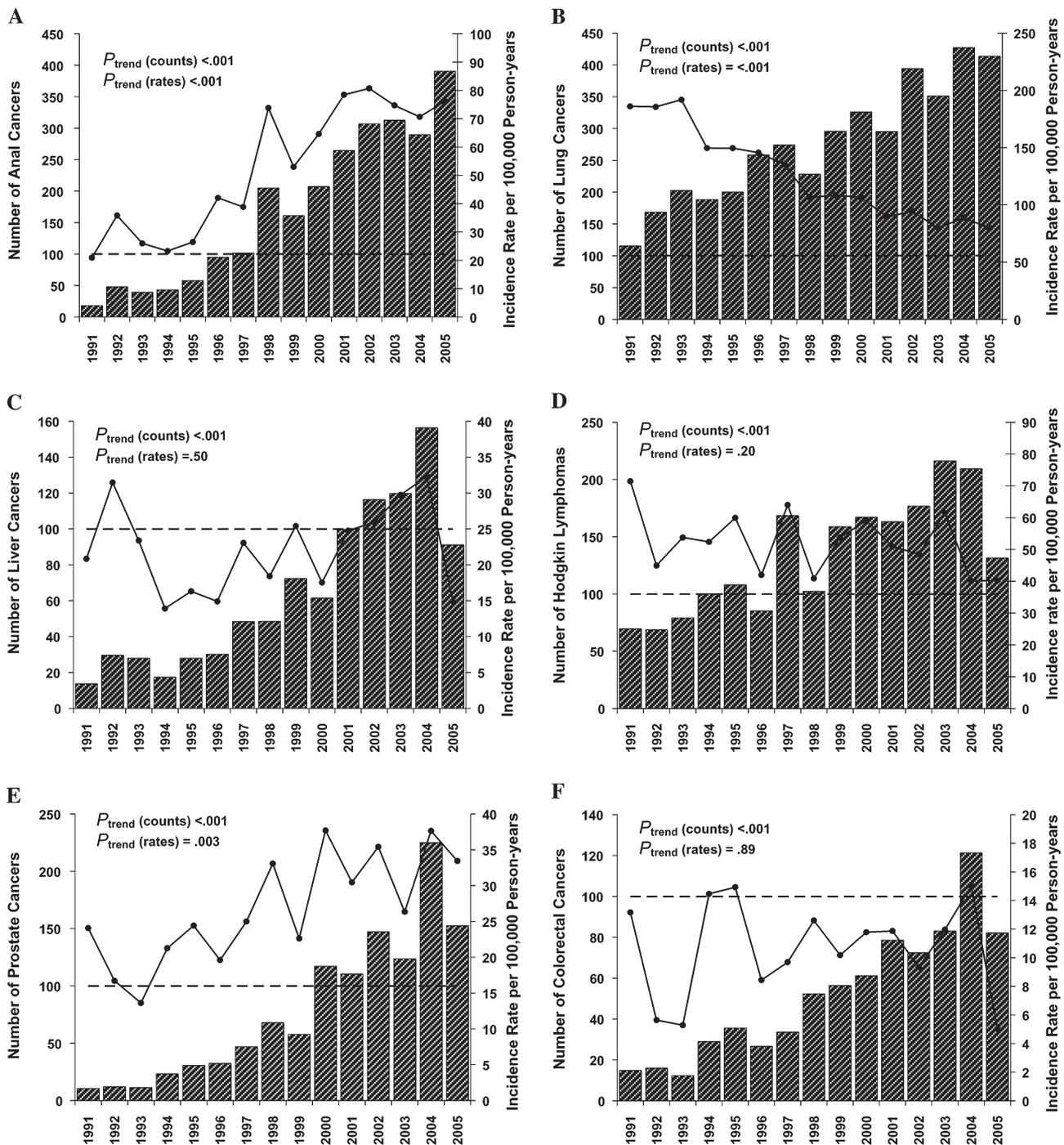


Figure 3. Cancer burden of selected non-AIDS-defining cancers among people living with AIDS in the United States during 1991–2005. **A)** Estimated counts (ie, number of cancers) and standardized incidence rates of anal cancer. **B)** Estimated counts and standardized incidence rates of lung cancer. **C)** Estimated counts and standardized incidence rates of liver cancer. **D)** Estimated counts and standardized incidence rates of Hodgkin lymphoma. **E)** Estimated counts and standardized

incidence rates of prostate cancer among men. **F)** Estimated counts and standardized incidence rates of colorectal cancer. **Bars** depict the estimated counts and **points connected by lines** depict incidence rates standardized to the 2000 US AIDS population by age group, race, and sex. The **horizontal dashed lines** represent a reference line corresponding to 100 cancers. Trends in cancer counts and rates were estimated with linear regression. Two-sided P values were calculated using the χ^2 test.

in incidence rates of prostate cancer among men with AIDS, which could reflect increases in prostate cancer screening (32). We also observed an increase in the burden of reproductive cancers in women, including cancers of the cervix and vulva (both caused by HPV), breast, and uterine corpus. This increase in the number of cervical cancers occurred despite a decline in the incidence rate.

Previous studies have not detected a change in cervical cancer incidence rates over time (1,4). The rise in the burden of reproductive cancers in women is in large part because of the increase in the number of women with AIDS, and as the population of women with AIDS continues to grow and age, these cancers will likely become a rising source of morbidity.

Cancers in people with HIV-only also represent an important part of the cancer burden, contributing 29.0% of all non-AIDS-defining cancers occurring in the HIV-infected population. As in the AIDS population, lung cancer was the most common non-AIDS-defining cancer in people with HIV-only. We were unable to estimate the number of non-AIDS-defining cancers that occurred in the entire HIV-only population in the United States or examine time trends, as our data on this population were more limited than for people with AIDS. Furthermore, our results underestimate the number of cancers occurring among people with HIV-only, as a substantial proportion of HIV cases are undiagnosed in the United States (21% in 2006) (34,35) and were not included in our calculations.

The growing burden of non-AIDS-defining cancers highlights the need for cancer prevention and early detection among HIV-infected people. In particular, programs focusing on smoking cessation (to prevent lung cancer and other cancers) and the prevention and treatment of hepatitis B and C viral infections (to prevent liver cancer) should be targeted toward HIV-infected people (36). HIV-infected women should be screened for cervical cancer according to specific guidelines (36). Given the increasing number of anal cancers in HIV-infected individuals, the efficacy of anal cancer screening with the Papanicolaou test needs to be further evaluated (37). In addition, our results highlight for clinicians that HIV-infected individuals need to receive screening for other common cancers (eg, colon, prostate, and breast cancer) based on the age-specific recommendations used in the general population (38). Finally, the growing cancer burden points to a continuing need for effective cancer treatment approaches tailored to HIV-infected people, and for the inclusion of HIV-infected individuals in clinical trials (39). HIV-related immune suppression and pharmacological interactions with HAART add complexity to cancer treatment, and outcomes are frequently poor (40,41). As individual centers may see few cancers in HIV-infected people, multicenter consortia are needed to comprehensively evaluate cancer treatment protocols in this population.

The major limitation of this study was the limited data for the HIV-only population. As a result, we applied a single rate for each cancer because data were too sparse to estimate rates separately in the strata described previously. Applying one rate assumes that the five registries with HIV-only data were representative of people in the 34 US states and that cancer rates were stable in this population during 1998–2007. Cancer registry data for the most recent calendar years for people with AIDS were also limited, as not all the registries included in the analysis had available data through 2005. The limited data for the most recent years led to unstable estimates for individual calendar years for some cancers. For example, cancer counts appeared to decrease in 2005 for liver cancer, Hodgkin lymphoma, prostate cancer, and colorectal cancer, but variance estimates for these counts were large (data not shown). Further linkages of population-based HIV and cancer registries will allow collection of additional data and continued monitoring of the cancer burden.

The use of HACM Study and CDC surveillance data to estimate cancer counts is the main strength of this study. The HACM Study includes cancer rates from a large and representative sample of HIV-infected people in the United States, and the CDC surveillance data include systematically collected national counts of AIDS

cases. These unique data resources allowed us to estimate annual cancer counts in people with AIDS in the United States over an extended time period.

In conclusion, though the risk of AIDS-defining cancers has declined dramatically over the years, KS and NHL remain the most common malignancies in the AIDS population in the United States. Additionally, the burden of non-AIDS-defining cancers has grown among HIV-infected people in the United States. This steep increase has largely been driven by the growth and aging of the HIV population, and for some cancers, by increasing incidence rates. The increase in cancer burden is not limited to cancers known to occur more frequently among HIV-infected people or to cancers with rising incidence rates. As the HIV-infected population in the United States continues to grow and age, cancer will emerge as an important public health issue.

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Affiliations of authors: Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD. Infections and Immunoepidemiology Branch (MSS, AKC, JJG, EAE) and Biostatistics Branch (RMP, MHG); Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA (HIH, JL); Office of HIV and AIDS Malignancy (KB, RY) and Center for Cancer Research (TSU), National Cancer Institute, Bethesda, MD.