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Title: Changing Temporal Trends in Non-AIDS Cancer Mortality among People Diagnosed with AIDS: San Francisco, California, 1996-2013

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Abstract

Background: Antiretroviral therapy (ART) has reduced AIDS-defining cancer (ADC) mortality, but its effect on non-AIDS-defining cancer (NADC) mortality is unclear. To help inform cancer prevention and screening, we evaluated trends in NADC mortality among people with AIDS (PWA) in the ART era.

Methods: This retrospective cohort study analyzed AIDS surveillance data, including causes of death from death certificates, for PWA in San Francisco who died in 1996-2013. Proportional mortality ratios (PMRs), and year, age, race, sex-adjusted standardized mortality ratios (SMRs) were calculated for 1996-1999, 2000-2005, and 2006-2013, corresponding to advances in ART.

Results: The study included 5,822 deceased PWA of whom 90% were male and 68% were aged 35-54 at time of death. Over time, the PMRs significantly decreased for ADCs (2.6%, 1.4%, 1.2%) and increased for NADCs (4.3%, 7.0%, 12.3%). For all years combined (1996-2013) and compared to the California population, significantly elevated SMRs were observed for these cancers: all NADCs combined (2.1), anal (58.4), Hodgkin lymphoma (10.5), liver (5.2), lung/larynx (3.0), rectal (5.2), and tongue (4.7). Over time, the SMRs for liver cancer (SMR 19.8, 11.2, 5.0) significantly decreased while the SMRs remained significantly elevated over population levels for anal (SMR 123, 48.2, 45.5), liver (SMR 19.8, 11.2, 5.0), and lung/larynx cancer (SMR 5.3, 4.7, 3.6).

Conclusion: A decline in ADC PMRs and increase in NADC PMRs represent a shift in the cancer burden, likely due to ART use. Moreover, given their elevated SMRs, anal, liver, and lung/larynx cancer remain targets for improved cancer prevention, screening, and

treatment.

Key words: AIDS; cancer; mortality; standardized mortality ratio (SMR); trends

1. Introduction

The use of effective antiretroviral therapy (ART) to control HIV infection has led to a dramatic reduction in HIV-related mortality, extending life expectancy among persons with HIV/AIDS to ages at which cancer incidence rapidly rises [1-7]. The combination of older age, immune perturbation, and prolonged exposure to carcinogens and oncogenic viral infections puts ART-treated adults at a heightened risk of cancer and cancer-related mortality [8, 9].

From the beginning of the AIDS epidemic, the cancers commonly reported as underlying and contributory causes of death among people with AIDS (PWA) were two AIDS-defining cancers (ADCs) – non-Hodgkin lymphoma (NHL) and Kaposi sarcoma (KS) [10, 11]. Now, with the widespread use of effective ART, non-AIDS-defining cancers (NADCs) have become increasingly more common as a cause of death among PWA [12, 13]. Although the use of ART has resulted in a decreased number of ADC deaths and increased life expectancy among PWA [6], the impact of ART on NADC mortality is less well known [13]. There are only a few recently published studies that have compared cancer-related morality in the United States (US) among PWA to that of the general population, particularly for NADCs, and even fewer studies that have assessed temporal trends in cancer mortality [12, 13].

In this investigation, we evaluated the changing impact of ART on NADC mortality

by examining temporal trends in NADC-related causes of death among San Francisco PWA from 1996 to 2013. We hypothesized that the proportion of ADC deaths would decrease as the proportion of NADC deaths increase over time commensurate with the increased use and potency of ART. We also hypothesized that the standardized mortality ratios (SMRs) for certain NADCs would be elevated above population levels as a result of longer life expectancies among PWA and contributory factors such as immune dysfunction, and prolonged exposure to cancer causing agents and viral infections.

2. Methods

2.1 Study population

We conducted a population-based retrospective cohort study of cancer-related mortality among PWA in San Francisco. In San Francisco, HIV/AIDS surveillance has been conducted through active and passive methods and, as of December 31, 2015, 15,995 people were reported living with HIV [14]. For this investigation we included all people diagnosed with AIDS (infected with HIV and have either a CD4+ T-cell count <200 cells/μL, a CD4+ T-cell percentage of total lymphocytes of <15%, or one of the AIDS-defining illnesses)[15] who were aged ≥15 years and who died from January 01, 1996 through December 31, 2013. The study excluded individuals with an HIV diagnosis who did not develop AIDS since name-based reporting of HIV infection began in 2006 and thus was not available for the entire study time period. Also excluded were children <15 years of age due to their low risk of cancer-related mortality.

2.2 Dependent and independent variables

Data on the date of AIDS diagnosis, demographic characteristics, HIV mode of transmission, country of origin, current address, and prescription of ART among PWA were ascertained through the San Francisco Department of Public Health (SFDPH) HIV/AIDS registry. Race was categorized as African American, Hispanic, Other (including multi-race), or White and age was categorized into 10-year age groups. We defined an individual as residing in an impoverished neighborhood at diagnosis if they lived in a census tract where >20% of persons aged 18 years of older had a median annual household income that was below the U.S. poverty level [16]. All independent variables used in these analyses were obtained at the time of diagnosis except for age, which was calculated as of the date of death.

Information on underlying and contributory causes of death was obtained from computer matches with the National Death Index (NDI), which included deaths through December 2013. For each decedent, underlying and contributory causes of death were classified as AIDS-defining cancer (ADC; KS, NHL, and invasive cervical cancer), cancers that meet the U.S. Centers for Disease Control and Prevention HIV stage 3 disease case definitions [10], non-AIDS-defining cancer (NADC), HIV/AIDS related non-cancer, or other. The frequencies of all underlying cancer causes of death were examined and those cancers that occurred in four or more persons were selected for cause-specific analyses.

2. 3 Statistical analysis

To explore temporal changes, we divided time into three calendar periods, which corresponded to the improvements in ART: 1996-1999 (early years of effective ART), 2000-2005 (following FDA approval of lopinavir/ritonavir—Kaletra® and tenofovir disoproxil fumarate—Viread®), and 2006-2013 (following FDA approval of multi-class combination medication). We analyzed changes in the distribution of socio-demographic, risk, survival, and treatment characteristics of our study population over the three time periods using the Maentel-Hanzel chi-square test for trends.

We also examined the number of underlying causes of deaths due to ADCs, NADCs, HIV/AIDS related non-cancers, and other conditions in each time period. The causes of death information on the death certificates [17] was summarized and coded using the International Classification of Diseases [18, 19]. A single underlying cause of death was identified from all reported conditions that began the chain of events that resulted in death using the NDI Automated Classification of Medical Entities computer program [20]. All coded conditions (including the underlying and contributory causes of death) listed on the death certificate were included in our multiple cause of death category.

Furthermore, we calculated proportional mortality ratios (PMRs) by calendar period for underlying and multiple causes of death. PMRs were expressed as a ratio of the number of deaths from a specific cause over the total number of deaths from all causes. We used chi-squared or Fisher's exact test to measure changes in PMRs across the three time periods. The PMR analyses were stratified by sex at birth. There were 181 transgender females (male to female) in our study sample and we categorized them by their sex at birth (male) because sex specific cancers such as prostate cancer are more closely associated with

anatomy than gender identity. There were no transgender males (female to male) in our study sample. Given the relatively low number of females in our study (n=499), we only reported female PMRs for all ADCs and all NADCs combined without a breakdown of specific cancer types.

Year-, age-, race-, and sex-adjusted SMRs with 95% Poisson confidence intervals were calculated for specific underlying NADC causes of death for all years combined (1996-2013) and then stratified by the three periods: 1996-1999, 2000-2005, and 2006-2013. The SMRs were calculated as the ratio of observed to expected number of deaths. The California population was our standard population for both number alive and cause-specific deaths [21, 22]. The expected deaths were calculated by multiplying the death rates of the California population by the total number of participants in the study population at the corresponding year, age, race, and sex group and summing up all the values for each group (using indirect standardization). Changes in the SMRs across the three time periods were measured using Poisson regression using a log of the expected counts as an offset. All analyses were performed using SAS® [23].

3. Results

3.1 Population characteristics

The study sample included 5,822 deceased PWA of whom 90% were male, 68% were aged 35-54 at time of death, 63% were White, and 59% were men who have sex with men (MSM). The distribution of socio-demographic, risk, and clinical characteristics of the study population changed significantly from 1996 to 2013 (Table 1). There were increases

in the proportions of females, decedents aged 45 to 94 years, persons who survived more than eight years post-AIDS diagnosis, non-Whites, MSM-PWID (MSM who also inject drugs), persons with non-U.S. country of origin, residents of impoverished neighborhoods and those who were prescribed ART.

Table 1. Study population characteristics by year of death, San Francisco AIDS cases.

Characteristics	1996-1999 Total n=2142 n (%)	2000-2005 Total n=1874 n (%)	2006-2013 Total n=1806 n (%)	1996-2013 Total n=5822 n (%)	P value[a]
Gender					<0.001
Female	123 (5.74)	158 (8.43)	162 (8.97)	443(7.61)	
Male	1991 (92.95)	1649 (87.99)	1573 (87.10)	5213 (89.53)	
Transgender	28 (1.31)	67 (3.58)	71 (3.93)	166 (2.85)	
Age at death (years old)					<0.001[b]
15-24	10 (0.47)	3 (0.16)	7 (0.39)	20 (0.34)	
25-34	306 (14.29)	113 (6.03)	60 (3.32)	479 (8.23)	
35-44	948 (44.26)	650 (34.69)	333 (18.44)	1931 (33.17)	
45-54	661 (30.86)	701 (37.41)	685 (37.93)	2047 (35.16)	
55-64	165 (7.70)	300 (16.01)	502 (27.80)	967 (16.61)	
65-94	52 (2.43)	107 (5.71)	219 (12.13)	378 (6.49)	
Number of months surviving since AIDS diagnosis					<0.001
0-23	571 (26.66)	339 (18.09)	266 (14.73)	1176 (20.20)	
24-47	726 (33.89)	224 (11.95)	147 (8.14)	1097 (18.84)	
48-71	504 (23.53)	295 (15.74)	147 (8.14)	946 (16.25)	
72-95	229 (10.69)	349 (18.62)	160 (8.86)	738 (12.68)	
>95	112 (5.23)	667 (35.59)	1086 (60.13)	1865 (32.03)	
Race/Ethnicity					<0.001
Black/African American	359 (16.76)	415 (22.15)	363 (20.10)	1137 (19.53)	
White/ Caucasian	1451 (67.74)	1144 (61.05)	1091 (60.41)	3686 (63.31)	
Hispanic	250 (11.67)	222 (11.85)	226 (12.51)	698 (11.99)	
Other	82 (3.83)	93 (4.96)	126 (6.98)	301 (5.17)	
Risk Group					<0.001
MSM	1419 (66.25)	1027 (54.80)	986 (54.60)	3432 (58.95)	
MSM + IDU	380 (17.74)	426 (22.73)	462 (25.58)	1268 (21.78)	
IDU only	291 (13.59)	346 (18.46)	283 (15.67)	920 (15.80)	
Other	52 (2.43)	75 (4.00)	75 (4.15)	202 (3.47)	

Country of origin					0.024
US	1961 (91.55)	1711 (91.30)	1611 (89.20)	5283 (90.74)	
Outside of US	181 (8.45)	163 (8.70)	195 (10.80)	539 (9.26)	
Residents of impoverished neighborhoods[c]					<0.001
Yes	518 (24.50)	600 (32.66)	577 (33.28)	1695 (29.82)	
No	1596 (75.50)	1237 (67.34)	1157 (66.72)	3990 (70.18)	
Prescribed ART					<0.001
Yes	1455 (67.93)	1552 (82.82)	1578 (87.38)	4585 (78.75)	
No/unknown	687 (32.07)	322 (17.18)	228 (12.62)	1237 (21.25)	

Abbreviations: n, number; ART, antiretroviral therapy; MSM, men who have sex with men; IDU, Injection drug use; US, United States

Chi-squared test.

[b] Fisher's exact test instead of chi square test.

[c] Missing data: 137 records with unknown income.

3.2 Overall distribution of deaths

The number of deaths in which an ADC was the underlying cause primarily decreased between the first two time periods and then remained relatively stable between 2000-2005 and 2006-2013 (p=0.002; Fig. 1). Meanwhile, the number of deaths from a NADC as the underlying cause increased over the three time periods from 93 to 132 to 222 (p<0.001). The number of deaths due to AIDS other than cancer decreased over the three time periods while deaths from non-AIDS-related underlying causes increased significantly.

3.3 Proportional mortality ratios—underlying causes of death

When stratified by sex, the PMRs for underlying causes of death for both ADCs and NADCs in females did not change significantly over time largely due to the small sample size (p=0.59 and 0.51, respectively; Table 2). Among males, the PMRs for ADCs significantly decreased for all ADCs combined (p=0.004) and for NHL (p<0.001), but not for KS (p=0.67; Table 2). In men, the PMRs significantly increased for certain NADCs, specifically, colon (p=0.01), liver (p=0.005), lung/larynx cancer (p<0.001), pancreas (p=0.005) and prostate (p=0.008) while the PMRs for anal cancer had a borderline significant increase (p=0.06).

3.4 Proportional mortality ratios—multiple causes of death

In females, the PMR trends for multiple causes of death were similar to that of the underlying causes and did not significantly change over time for ADCs and NADCs (p=0.39 and 0.47, respectively; Table 2). The PMRs for multiple causes of death in males were significant for several cancers (Table 2). Most notably, the PMRs significantly decreased for both KS and NHL (from 11.94% in years 1996-1999 to 2.86% in years 2006-2013, and from 10.80% in years 1996-1999 to 6.33% in years 2006-2013, respectively; p<0.001). Moreover, the PMRs significantly increased for anal cancer (p=0.03) in addition to colon (p=0.02), liver (p<0.001), lung/larynx (p<0.001), pancreas (p<0.001) and prostate cancer (p=0.002).

Table 2. Proportional morality ratios (PMRs) for cancer-related underlying and multiple causes of death among people diagnosed with AIDS in San Francisco.

	Female			
	Year of death			
Cause of death	**1996-1999 Total n=123 n (%)**	**2000-2005 Total n=158 n (%)**	**2006-2013 Total n=162 n (%)**	**P value[a]**
ADCs (all)				
UCOD	2 (1.63)	3 (1.90)	1 (0.62)	0.59
MCOD[b]	3 (2.44)	9 (5.70)	8 (4.94)	0.39
NADCs (all)				
UCOD	2 (1.63)	6 (3.80)	7 (4.32)	0.51
MCOD	4 (3.25)	10 (6.33)	10 (6.17)	0.47
	Male			
	Year of death			
Cause of death	**1996-1999 Total n=2019 n (%)**	**2000-2005 Total n=1716 n (%)**	**2006-2013 Total n=1644 n (%)**	**P value[a]**
ADCs (all)				
UCOD	53 (2.63)	24 (1.40)	21 (1.28)	0.004
MCOD	430 (21.30)	223 (13.00)	147 (8.94)	<0.001
Kaposi sarcoma				
UCOD	3 (0.15)	5 (0.29)	4 (0.24)	0.67
MCOD	241 (11.94)	80 (4.66)	47 (2.86)	<0.001
Non-Hodgkin lymphoma				
UCOD	50 (2.48)	19 (1.11)	17 (1.03)	<0.001
MCOD	218 (10.80)	147 (8.57)	104 (6.33)	<0.001
NADCs (all)				
UCOD	91 (4.51)	126 (7.34)	215 (13.08)	<0.001
MCOD	172 (8.52)	182 (10.61)	296 (18.00)	<0.001
Anal				
UCOD	7 (0.35)	7 (0.41)	15 (0.91)	0.06
MCOD	9 (0.45)	13 (0.76)	20 (1.22)	0.03
Bladder				
UCOD	2 (0.10)	2 (0.12)	4 (0.24)	0.56
MCOD	3 (0.15)	3 (0.17)	6 (0.36)	0.39
Brain				
UCOD	4 (0.20)	3 (0.17)	6 (0.36)	0.54
MCOD	5 (0.25)	5 (0.29)	6 (0.36)	0.78
Colon				
UCOD	2 (0.10)	4 (0.23)	11 (0.67)	0.01
MCOD	3 (0.15)	5 (0.29)	12 (0.73)	0.02
Esophageal				

UCOD	2 (0.10)	1 (0.06)	6 (0.36)	0.10
MCOD	2 (0.10)	2 (0.12)	7 (0.43)	0.08
Hodgkin lymphoma				
UCOD	4 (0.20)	1 (0.06)	4 (0.24)	0.41
MCOD	7 (0.35)	7 (0.41)	15 (0.91)	0.06
Kidney				
UCOD	2 (0.10)	4 (0.23)	5 (0.30)	0.38
MCOD	2 (0.10)	5 (0.29)	5 (0.30)	0.29
Leukemia				
UCOD	2 (0.10)	2 (0.12)	5 (0.30)	0.31
MCOD	8 (0.40)	5 (0.29)	11 (0.67)	0.26
Liver				
UCOD	16 (0.79)	27 (1.57)	33 (2.01)	0.005
MCOD	20 (0.99)	31 (1.81)	44 (2.68)	<0.001
Lung/larynx[c]				
UCOD	22 (1.09)	40 (2.33)	64 (3.89)	<0.001
MCOD	26 (1.29)	44 (2.56)	73 (4.44)	<0.001
Melanoma				
UCOD	2 (0.10)	4 (0.23)	6 (0.36)	0.25
MCOD	2 (0.10)	5 (0.29)	7 (0.43)	0.14
Pancreas				
UCOD	0 (0.00)	3 (0.17)	7 (0.43)	0.005
MCOD	0 (0.00)	3 (0.17)	10 (0.61)	<0.001
Prostate				
UCOD	1 (0.05)	3 (0.17)	9 (0.55)	0.008
MCOD	1 (0.05)	5 (0.29)	11 (0.67)	0.002
Rectal				
UCOD	4 (0.20)	7 (0.41)	8 (0.49)	0.27
MCOD	5 (0.25)	12 (0.70)	11 (0.67)	0.08
Stomach				
UCOD	1 (0.05)	1 (0.06)	4 (0.24)	0.26
MCOD	1 (0.05)	3 (0.17)	4 (0.24)	0.26
Testis				
UCOD	3 (0.15)	0 (0.00)	1 (0.06)	0.33
MCOD	3 (0.15)	0 (0.00)	2 (0.12)	0.34
Tongue				
UCOD	2 (0.10)	2 (0.12)	4 (0.24)	0.56
MCOD	2 (0.10)	2 (0.12)	4 (0.24)	0.56

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2 Abbreviations: ADC, AIDS-defining cancer; NADC, non-AIDS-defining cancer; UCOD,

underlying cause of death; MCOD, multiple cause of death.

[a]Fisher's exact test.

[b] Individuals may have more than one cause of death.

[c] Larynx only in males: UCOD—0 case (1996-1999), 3 cases (2000-2005), 1 case (2006-2013); MCOD—0 case (1996-1999), 4 cases (2000-2005), 2 cases (2006-2013).

3.5 Standardized mortality ratios

The study sample contributed a total of 250,254 person-years of observation. For all years combined (1996-2013), significantly elevated SMRs were observed for all NADCs combined (2.1), anal cancer (58.4), Hodgkin lymphoma (10.5), liver cancer (5.2), lung/larynx cancer (3.0), rectal cancer (5.2), and tongue cancer (4.7).

When stratified by the three time periods, the SMRs for all NADCs combined significantly decreased ($p<0.001$, Table 3). However, only one of the NADC-specific SMR trends changed significantly over time: the SMRs for liver cancer decreased (19.80, 11.16, 4.95, respectively; $p<0.001$). Still, the SMRs were significantly elevated among PWA compared to the general population for anal, liver, and lung/larynx cancer during the entire study period as well as rectal cancer in 2000-2013.

Table 3. Year, age, race, sex-adjusted standardized mortality ratios (SMRs) for underlying causes of death among people diagnoses with AIDS in San Francisco.

	Year of death				
Cause of	**All years**	**1996-1999**	**2000-2005**	**2006-2013**	**P**

death[a]	combined (1996-2013)				value[b]
NADCs (all)					<0.001
Observed	447	93	132	222	
Expected	214.67	25.97	57.89	120.06	
SMR (CI)	2.08 (1.89-2.28)	3.58 (2.85-4.31)	2.28 (1.89-2.67)	1.85 (1.61-2.09)	
Anal					0.07
Observed	29	7	7	15	
Expected	0.50	0.06	0.15	0.33	
SMR (CI)	58.36 (37.12-79.60)	122.8 (31.83-231.8)	48.24 (12.50-83.97)	45.53 (22.49-68.57)	
Bladder					0.23
Observed	8	2	2	4	
Expected	4.91	0.33	0.86	2.13	
SMR (CI)	1.63 (0.50-2.76)	6.00 (0-14.31)	2.32 (0-5.54)	1.88 (0.04-3.72)	
Brain					0.28
Observed	14	4	3	7	
Expected	9.58	1.14	2.29	4.53	
SMR (CI)	1.46 (0.70-2.23)	3.51 (0.07-6.95)	1.31 (0-2.79)	1.54 (0.4-2.69)	
Colon					0.70
Observed	17	2	4	11	
Expected	16.57	1.85	4.26	8.74	
SMR (CI)	1.03 (0.54-1.51)	1.08 (0-2.59)	0.94 (0.02-1.86)	1.26 (0.51-2.00)	
Esophageal					0.86
Observed	9	2	1	6	
Expected	8.58	0.63	1.46	3.2	
SMR (CI)	1.05 (0.36-1.73)	3.17 (0-7.56)	0.69 (0-2.03)	1.88 (0.38-3.38)	
Hodgkin lymphoma					0.41
Observed	9	4	1	4	
Expected	0.86	0.16	0.24	0.32	
SMR (CI)	10.47 (3.63-12.31)	24.41 (0.49-48.33)	4.15 (0-12.29)	12.38 (0.25-24.52)	

Kidney					0.36
Observed	11	2	4	5	
Expected	7.02	0.62	1.41	2.95	
SMR (CI)	1.57 (0.64-2.49)	3.24 (0-7.73)	2.82 (0.06-5.59)	1.69 (0.21-3.18)	
Leukemia					0.66
Observed	9	2	2	5	
Expected	8.53	0.99	2.05	4.14	
SMR (CI)	1.05 (0.37-1.74)	2.03 (0-4.84)	0.98 (0-2.33)	1.21 (0.15-2.26)	
Liver					<0.001
Observed	78	17	27	34	
Expected	15.01	0.86	2.42	6.87	
SMR (CI)	5.20 (4.04-6.34)	19.80 (10.39-29.21)	11.16 (6.95-15.38)	4.95 (3.29-6.61)	
Lung/larynx[c]					0.06
Observed	133	22	45	66	
Expected	44.62	4.13	9.60	18.58	
SMR (CI)	2.98 (2.47-3.49)	5.32 (3.10-7.55)	4.69 (3.32-6.06)	3.55 (2.69-4.41)	
Melanoma					0.75
Observed	12	2	4	6	
Expected	6.26	0.73	1.37	2.62	
SMR (CI)	1.92 (0.83-3.00)	2.75 (0-6.56)	2.91 (0.58-5.77)	2.29 (0.46-4.13)	
Pancreas					0.83
Observed	12	1	4	7	
Expected	15.05	1.31	3.34	8.36	
SMR (CI)	0.80 (0.35-1.25)	0.76 (0-2.26)	1.20 (0.02-2.37)	0.84 (0.22-1.46)	
Prostate					0.69
Observed	13	1	3	9	
Expected	11.45	0.62	1.46	3.8	
SMR (CI)	1.14 (0.52-1.75)	1.61 (0-4.75)	2.06 (0-4.38)	2.37 (0.82-3.91)	
Rectal					0.08
Observed	19	4	7	8	
Expected	3.62	0.34	0.78	1.8	
SMR (CI)	5.24	11.81	8.95	4.46	

	(2.89-7.60)	(0.24-23.39)	(2.32-15.59)	(1.37-7.55)	
Stomach					0.81
Observed	6	1	1	4	
Expected	6.81	0.74	1.61	3.07	
SMR (CI)	0.88 (0.18-1.58)	1.35 (0-4.01)	0.62 (0-1.84)	1.30 (0.03-2.58)	
Testis					0.11
Observed	4	3	0	1	
Expected	0.64	0.07	0	0.15	
SMR (CI)	6.20 (0.12-12.29)	43.88 (0-93.53)	0	6.85 (0-20.27)	
Tongue					0.42
Observed	8	2	2	4	
Expected	1.69	0.16	0.34	0.70	
SMR (CI)	4.74 (1.46-8.02)	12.89 (0-30.75)	5.83 (0-13.92)	5.69 (0.11-11.26)	

Abbreviation: NADC, non-AIDS-defining cancer; SMR, standardized mortality ratio; CI, 95% confidence interval.

Number of expected deaths was rounded to two decimal places.

[b] Poisson regression for change in SMRs across the three time periods, fixed effects.

[c] Larynx only (observed): 0 case (1996-1999), 6 cases (2000-2005), 1 case (2006-2013).

4. Discussion

We observed a dramatic decrease in both the number and the proportion of deaths due to ADCs and an increase in both the number and the proportion of deaths due to NADCs among PWA since the introduction of ART in 1996, as hypothesized. Among males, these trends were seen for cancers listed as either the underlying cause or other

contributory cause of death on the death certificate, giving further support to our hypotheses.

Even though the year, age, race, and sex-adjusted SMRs for NADCs significantly decreased over the three time periods, the SMRs remained elevated for select NADCs (anal, liver, and lung/larynx) among PWA compared to the general population. For Hodgkin lymphoma, rectal, and tongue cancer, the SMRs were also significant for all years combined but failed to show a significant change over time – perhaps due to too few observations in the three time periods. A recent and large population-based registry study that linked HIV/AIDS and cancer registry data found that one-third of the rectal squamous cell carcinoma's (SCC) of the anus were misclassified as rectal SCC [24]. This suggests it is possible that some of the anal cancers may have been misclassified as rectal cancer on the death certificates and, if so, the SMRs for anal cancer would be even higher and rectal cancer lower.

A few hypotheses have been proposed to explain the mechanism by which use of ART may contribute to the decline in the SMRs for the NADCs. Use of ART reduces the HIV viral burden allowing the immune system to reconstitute, thus reducing immune deficiency-related deaths [25-27]. Additionally, recent HIV treatment guidelines recommend newer classes of ART such as integrase inhibitor as first line treatment, which have fewer drug-drug interactions with chemotherapy compared to older protease inhibitors [28, 29]. Clinicians are now more likely to continue ART during cancer treatment than in the past which results in longer overall survival thus resulting in fewer cancer-related causes of death [30].

Other studies have examined the effect of risk factors other than immunosuppression on the development of liver, lung, and anal cancer. The increased risk of liver cancer is associated with excessive alcohol consumption and hepatitis B and C co-infections [31-33], behaviors and infections that are more common among PWA than in the general population [31, 34-36]. The high prevalence of smoking in PWA certainly contributes to excess lung cancer risk, though it may not entirely account for the increased rate of lung cancer in PWA [37-40]. The excess incidence of anal cancer has been associated with an increased prevalence of oncogenic anal human papillomavirus (HPV) infection among HIV infected individuals, especially men who had sex with men [41]. Evidence has demonstrated a role of immunosuppression in cultivating the spread of HPV [42]. Therefore, the impact of immunosuppression on mortality for each NADC may differ since development of NADCs appears multifactorial.

A limited number of studies that also examined SMRs for NADCs reported similar results. One Italian study of PWA observed significantly elevated SMRs during 2006-2011 for the following NADCs when compared to the general population of Italy: anal (SMR=228), Hodgkin lymphoma (SMR=122), unspecified uterus (SMR=52.5), liver (SMR=13.2), skin melanoma (SMR=10.9), lung (SMR=8.0), head and neck (SMR=7.8), leukemia (SMR=7.6), and colon-rectal (SMR=5.4) [43]. To our knowledge only one US study compared NADC mortality among PWA to people without AIDS, this study included people living with HIV and HIV-uninfected individuals. That study reported significantly elevated hazard ratios (HR) in PWA compared to people without AIDS for risk of death from Hodgkin lymphoma (HR=2.6, 95% CI=1.7-4.1), larynx (HR=4.0, 95% CI=1.9-8.3),

and lung (HR=2.5, 95% CI=2.0-3.1) cancer in New York City from 1996-2000 [44]. The variation in results among these studies could be attributed to differences in study time period, location, population and relative measures (i.e. SMR vs. HR).

There were limitations to this study that require consideration. First, our data were derived from one geographic region where males accounted for the vast majority of the AIDS cases. However, our large sample and comprehensive data from San Francisco provide robust estimates for PWA in cities where the epidemic is concentrated among MSM. Second, the mortality information originated from death certificates, which may underreport causes of death especially if there are multiple morbidities or may misclassify causes of death if the disease is associated with social stigma. Nevertheless, studies have shown that cancer causes of death are less likely to be underreported compared to other causes such as infection [45-47]. Third, the study population was restricted to people diagnosed with AIDS and thus the results may not be applicable to people with HIV infection who have not been diagnosed with AIDS. However, because surveillance name-based reporting of HIV infection was not required until the mid-2000's, by restricting our study sample to those diagnosed with AIDS, we were able to examine the changing impact of ART on cancer mortality during the entire ART time period (1996-2013). Finally, although we had data on when ART was first prescribed, we lacked a direct measure of ART use or adherence, and thus relied on calendar periods as a surrogate for an increase in use and improvements in ART.

Despite the above limitations, our study had several notable strengths. First, our data was matched with the NDI and evidence has shown that linking death certificate data

with NDI improved accuracy of population-based cancer survival rate measurements [48]. Our methodology for analyzing cause of death data from death certificates was also standardized and has been utilized by other studies, thus facilitating a direct comparison of our study results to that of other studies. Finally, our mortality data included the early ART era and extended to 2013, thus allowing us to evaluate, indirectly, the impact of ART and of treatment policies that call for earlier initiation of ART (such as "Test and Treat") to further prevent HIV/AIDS related deaths [49].

Compared to the California population, mortality rates for anal, liver, lung /larynx, and rectal cancer remained significantly elevated in PWA during the most current ART period, years 2006-2013. For some of these cancers, significant progress has been made in cancer prevention and treatment including the HPV vaccine for prevention of anal and cervical cancer, smoking cessation for the prevention of lung/larynx cancer, and hepatitis B virus (HBV) vaccination and HBV and hepatitis C virus treatment for prevention of liver cancer. As had been previously demonstrated, use of and adherence to ART will also help prevent certain ADCs [50-53].

Regarding cancer screening interventions specific to people living with HIV, the information is limited. In the US there are guidelines for cancer screening in the general population that are derived via expert opinion regarding the best available scientific evidence, and these guidelines are regularly updated and incorporate a rigorous evaluation of the benefits and harms of screening procedures [54, 55]. Presently, there are data indicating that the approach to screening for at least three of the most common NADCs (anal, liver, and lung cancer) in the general population may require adaptation for people

living with HIV infection because of the increased risk associated with HIV, as well as the behaviors and conditions that are prevalent among those with HIV [56, 57]. Deciding when and how to screen people living with HIV for cancer is complex and should consider the risk of the particular cancer, the life expectancy of the patient, and the benefits and harms that may result from the screening intervention [56].

In summary, by analyzing this large population-based HIV/AIDS surveillance registry data and utilizing up-to-date mortality data, our study helped identify cancers that should be considered for increased prevention, screening, and early detection as part of standard of care for people living with HIV. Future research is still needed to explore NADC mortality among all people with HIV infection to determine if the cancer mortality trends we observed among PWA are similar to those in HIV-infected people without AIDS.

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