Cancer risk and prevention in persons living with HIV/AIDS (PLWHA)

Robert Dubrow, MD, PhD
Professor of Epidemiology
Yale School of Public Health

Main collaborators

- Lesley Park
- Janet Tate
- Amy Justice
- Michael Silverberg
- Li Qin
- Haiqun Lin

Cancer risk and prevention in PLWHA

- Cancer is a major cause of morbidity and mortality in PLWHA
- PLWHA have elevated risk for many cancer types, especially those with a viral etiology, due to
  - HIV infection itself
  - High prevalence of non-HIV cancer risk factors
- Cancer prevention among PLWHA
  - Early antiretroviral therapy (ART) to preserve/restore immune function
  - Reduction in prevalence of non-HIV cancer risk factors
  - Screening for selected cancer types

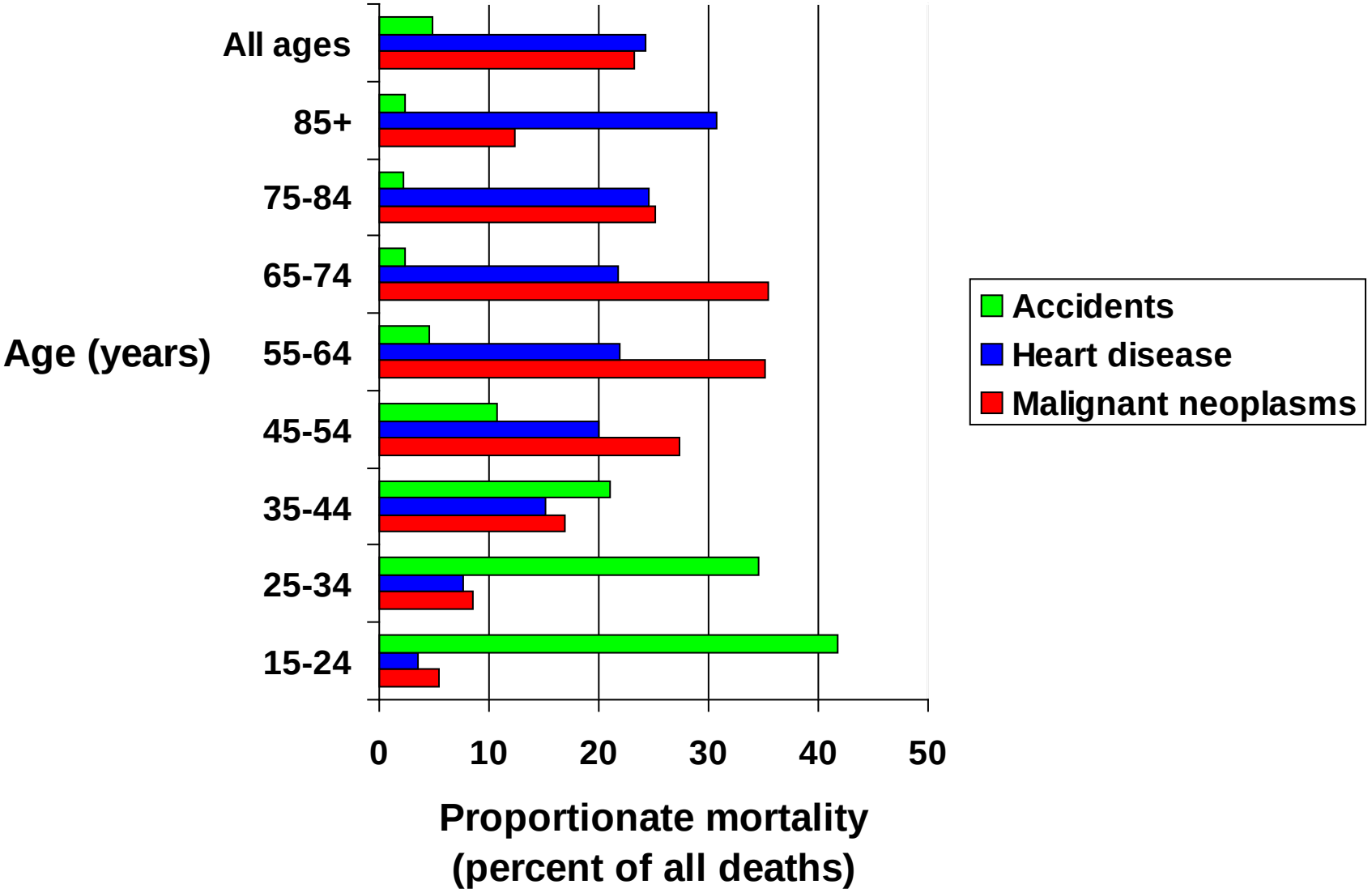
Cancer risk and prevention in PLWHA

- Cancer is a major cause of morbidity and mortality in PLWHA
- PLWHA have elevated risk for many cancer types, especially those with a viral etiology, due to
  - HIV infection itself
  - High prevalence of non-HIV cancer risk factors
- Cancer prevention among PLWHA
  - Early ART to preserve/restore immune function
  - Reduction in prevalence of non-HIV cancer risk factors
  - Screening for selected cancer types

Cancer is a major cause of morbidity and mortality in the general US population

Proportionate mortality, US, 2010

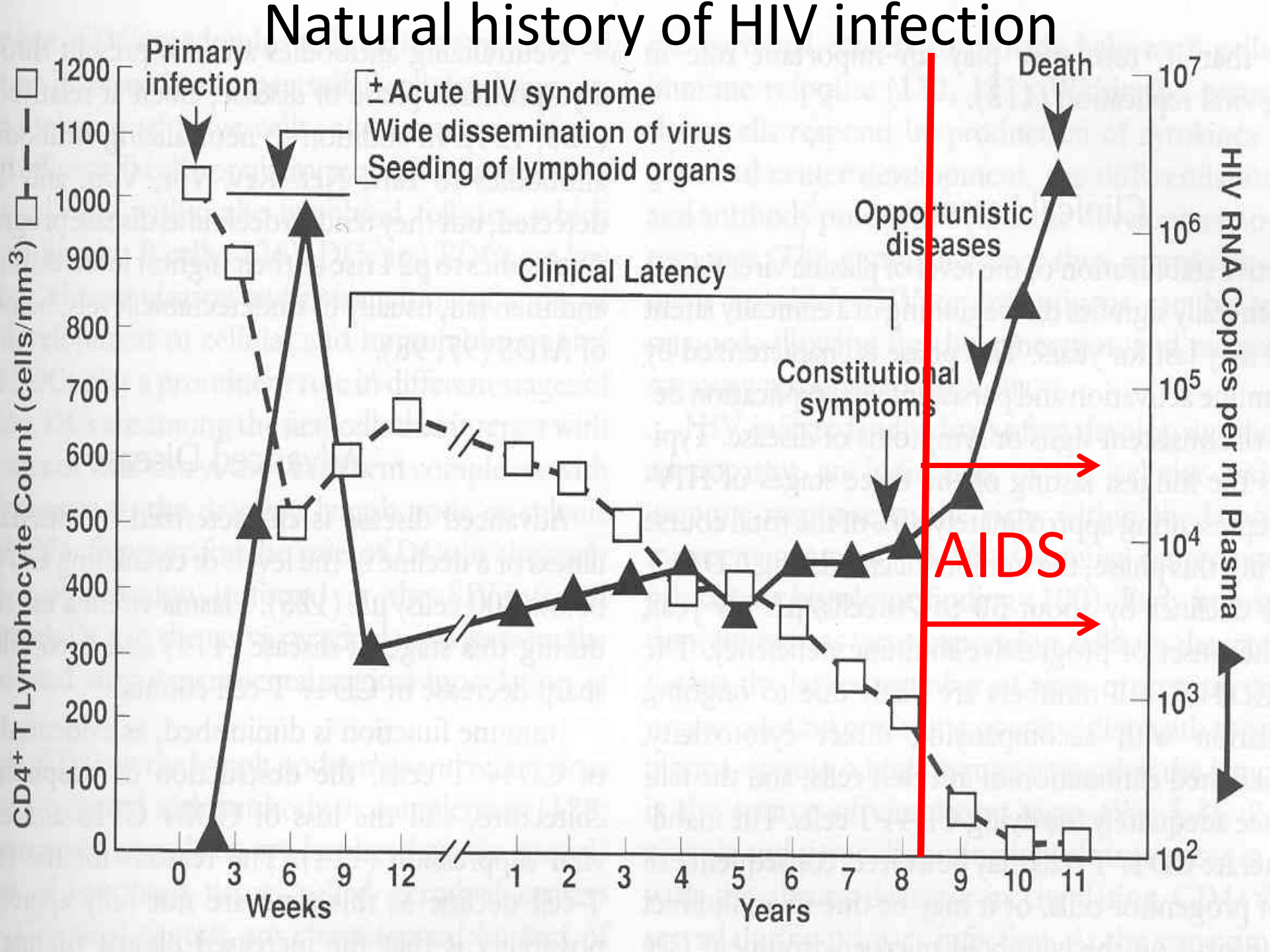
(adapted from Murphy SL, et al. Deaths: final data for 2010. National vital statistics reports; vol 61 no 4. NCHS, 2013)



Classification of cancers in HIV

- AIDS-defining cancers (ADC)
  - Kaposi sarcoma (KS)
  - Non-Hodgkin lymphoma (NHL)
  - Invasive cervical cancer (ICC)
- Non-AIDS-defining cancers (NADC)

Natural history of HIV infection



AIDS: end stage of HIV infection

- HIV seropositivity

AND

- CD4 cell count <200 cells/ml blood

OR

- One or more AIDS-defining condition
  - Opportunistic infections
  - Cancers
  - Other

- In the pre-ART era, most PLWHA died of AIDS

AIDS-Defining Conditions: Other

- Encephalopathy, HIV-related
- HIV wasting syndrome

AIDS-Defining Conditions: opportunistic infections (1)

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (> 1 month duration)
- Cytomegalovirus disease (other than liver, spleen, or lymph nodes)
- Cytomegalovirus retinitis (with loss of vision)

AIDS-Defining Conditions: opportunistic infections (2)

- Herpes simplex virus: chronic ulcer(s) (> 1 month duration) or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (> 1 month duration)
- *Mycobacterium avium* complex or *M. kansasii*, disseminated or extrapulmonary

AIDS-Defining Conditions: opportunistic infections (3)

- *Mycobacterium tuberculosis*, any site
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jirovecii* pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain

AIDS-Defining Conditions: cancers

- KS
  - Caused by KS-associated herpesvirus (KSHV)
- NHL
  - Lymphoma, Burkitt's
  - Lymphoma, immunoblastic
  - Lymphoma, primary, of brain
  - HIV-associated subtypes caused by Epstein-Barr virus (EBV)
- ICC
  - Caused by human papillomavirus (HPV)

HIV in the ART era (1996 onward)

- Substantial increase in life expectancy
- Substantial increase in non-AIDS co-morbidities
- Shift in cause of death spectrum toward non-AIDS-defining causes, including NADC

Time trends of cancer mortality among men in the Veterans Aging Cohort Study (VACS) Virtual Cohort

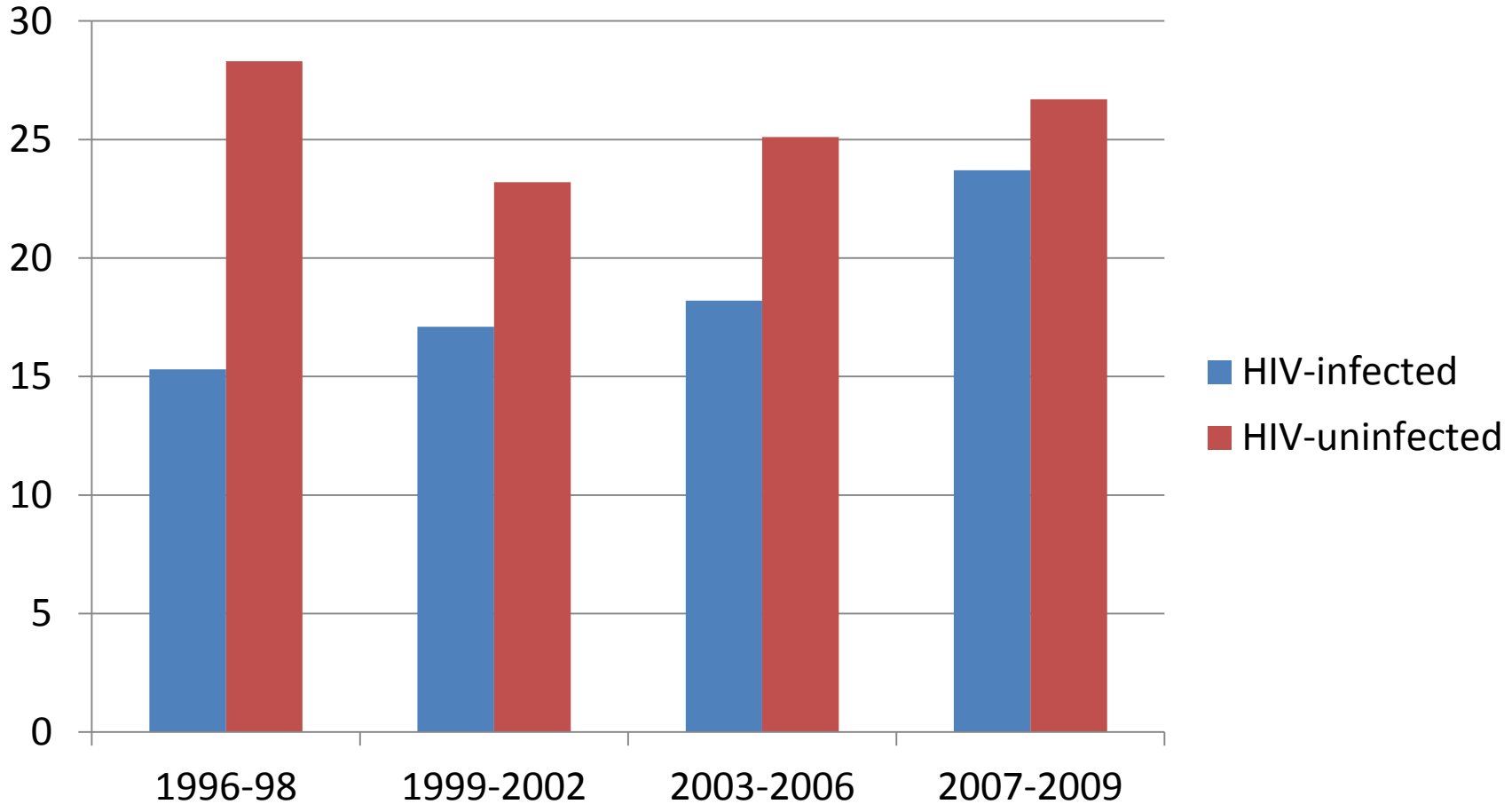
VACS Virtual Cohort

- Assembled from national VA databases
  - No contact with patients
  - Linkage accomplished using scrambled Social Security Number as personal identifier
- Periodically updated open cohort with earliest enrollment in 1996
- ~48,000 HIV-infected veterans
- ~96,000 HIV-uninfected veterans, matched to HIV-infected veterans by age, sex, race/ethnicity, and VA site

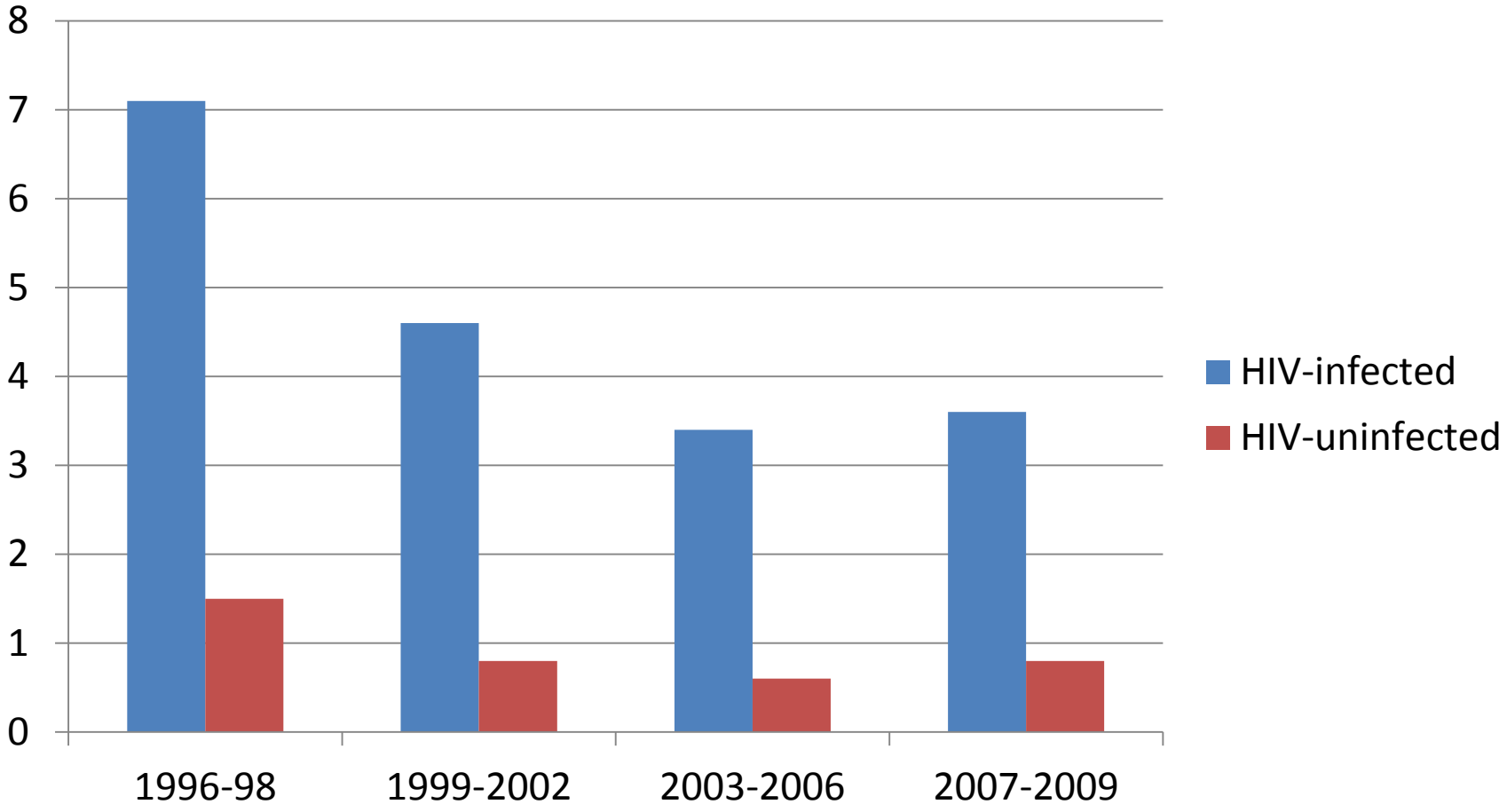
Time trends of cancer mortality among men in the VACS Virtual Cohort

- Linked VACS with the National Death Index to obtain causes of death, 1996-2009
- Median observation time
  - HIV-infected: 6.4 years
  - HIV-uninfected: 8.3 years
- 27,195 deaths

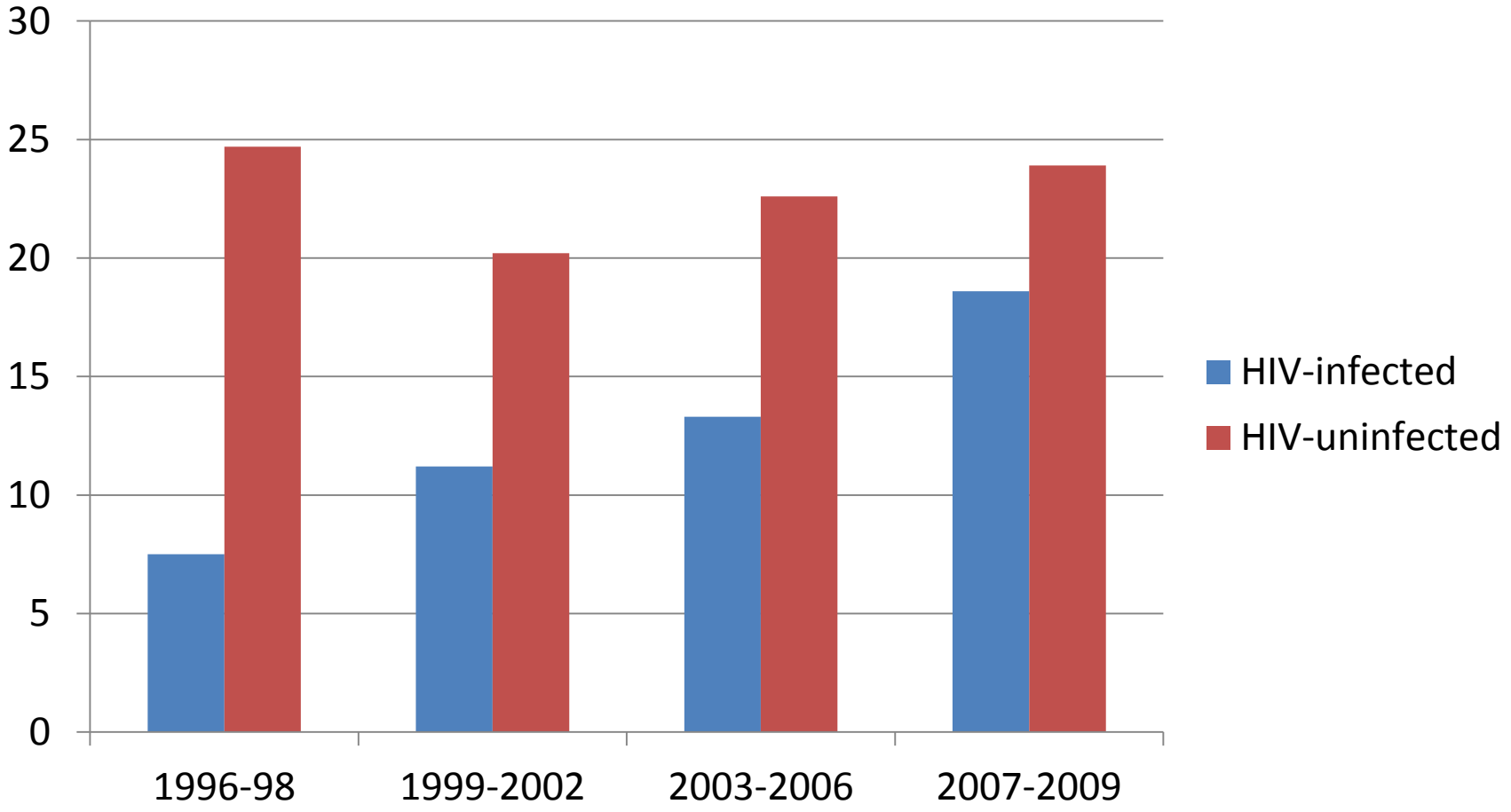
Time trends in cancer proportionate mortality (deaths with cancer/all deaths [%])



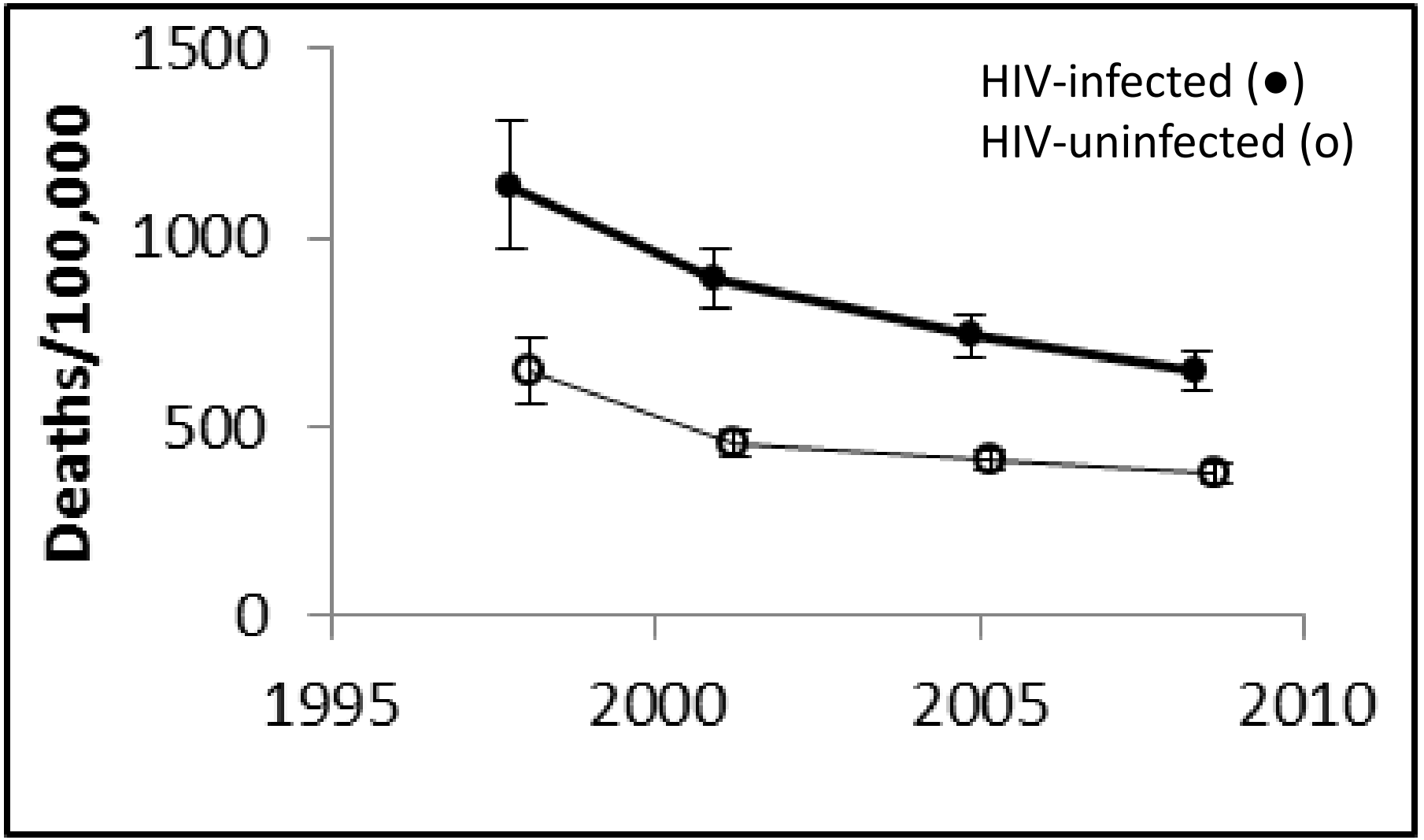
Time trends in ADC proportionate mortality (deaths with ADC/all deaths [%])



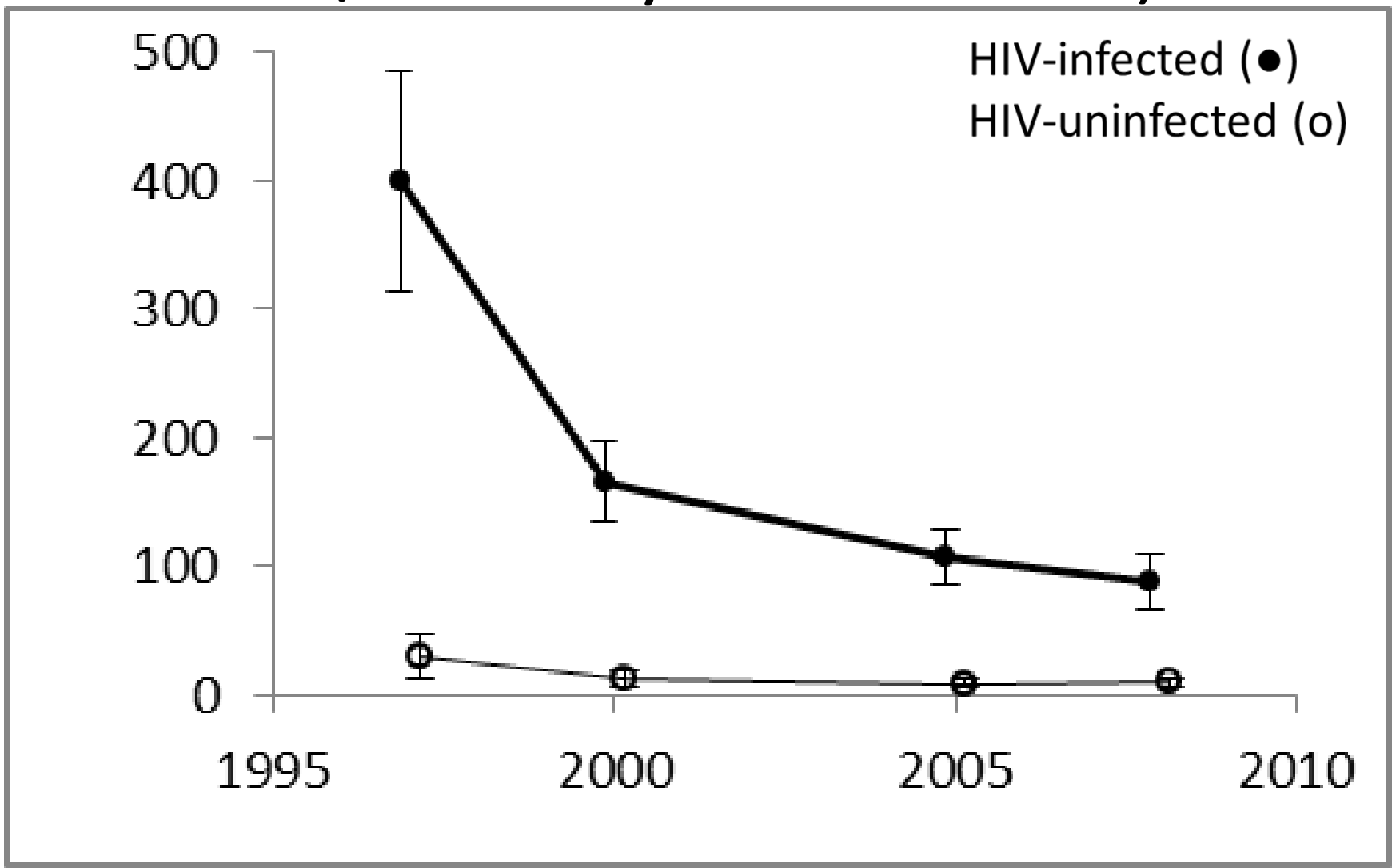
Time trends in NADC proportionate mortality (deaths with NADC/all deaths [%])



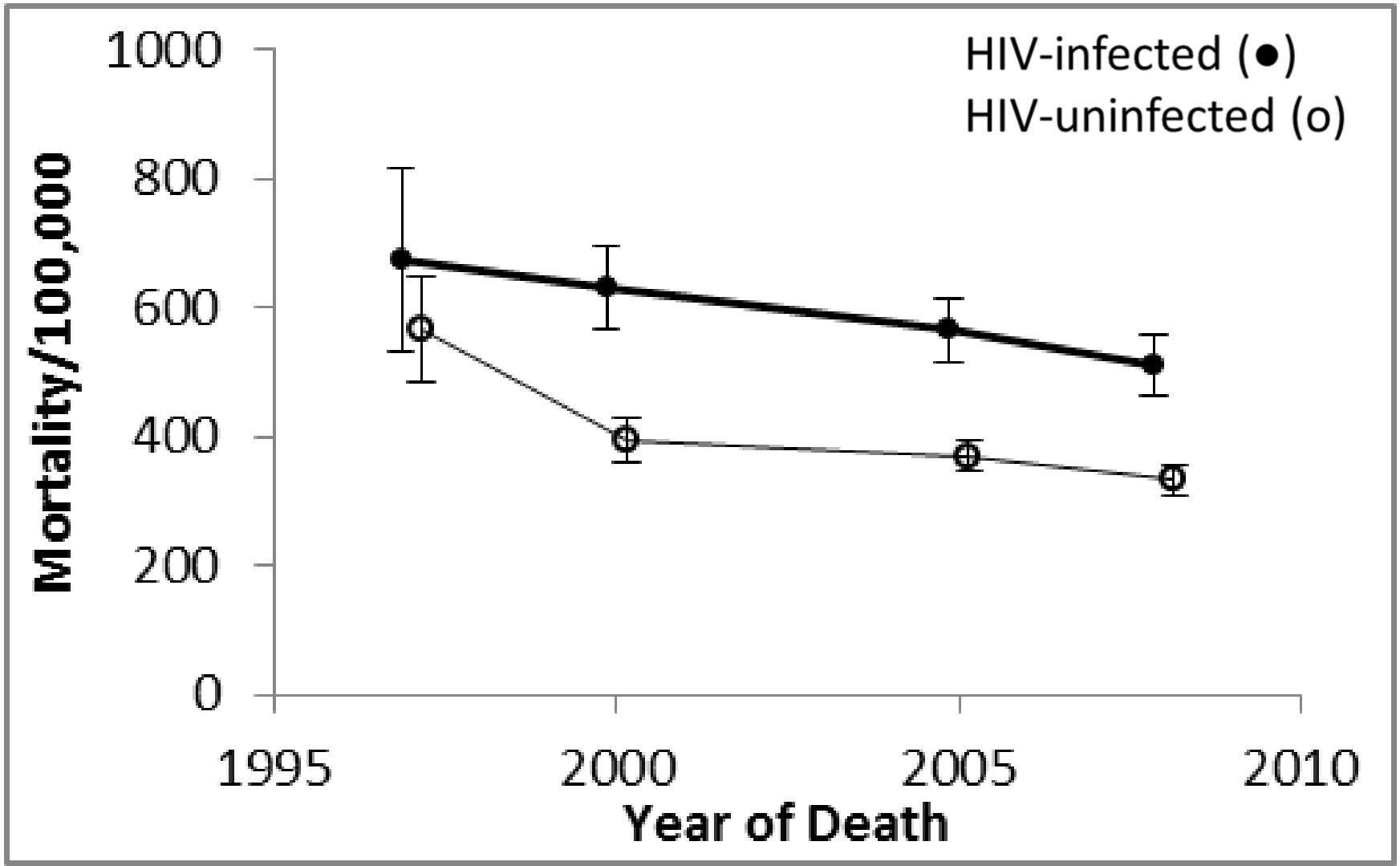
Time trends in underlying cause cancer mortality rates (age- and race/ethnicity standardized)



Time trends in underlying cause ADC mortality rates (age- and race/ethnicity standardized)



Time trends in underlying cause NADC mortality rates (age- and race/ethnicity standardized)



Time trends of cancer mortality among men in the VACS: conclusions

- Cancer proportionate mortality among PLWHA is approaching that in the HIV-uninfected population
- Cancer mortality rates are about 1.7-fold higher in HIV-infected persons compared to HIV-uninfected persons

Cancer risk and prevention in PLWHA

- **Cancer is a major cause of morbidity and mortality in PLWHA**
- PLWHA have elevated risk for many cancer types, especially those with a viral etiology, due to
  - HIV infection itself
  - High prevalence of non-HIV cancer risk factors
- Cancer prevention among PLWHA
  - Early ART to preserve/restore immune function
  - Reduction in prevalence of non-HIV cancer risk factors
  - Screening for selected cancer types

Cancer incidence in HIV-infected compared to HIV-uninfected veterans in the VACS Virtual Cohort

- Linked VACS with VA Central Cancer Registry to obtain cancer diagnoses
- Age-, sex-, race/ethnicity- and calendar-period-standardized incidence rate ratios (IRR) (HIV-infected vs. HIV-uninfected)

IRRs (HIV-infected vs. HIV-uninfected) for specific cancer types (1)

Cancer	IRR	95% CI
All	1.93	1.82, 2.05
Oral cavity & pharynx	1.30	1.03, 1.64
Esophagus	0.89	0.59, 1.34
Stomach	1.03	0.62, 1.72
Colorectal	1.22	0.97, 1.52

IRRs (HIV-infected vs. HIV-uninfected) for specific cancer types (2)

Cancer	IRR	95% CI
Anal	28.14	16.06, 49.32
Liver	3.27	2.50, 4.29
Pancreas	1.31	0.84, 2.03
Larynx	1.37	0.98, 1.91
Lung	1.87	1.63, 2.14

IRRs (HIV-infected vs. HIV-uninfected) for specific cancer types (3)

Cancer	IRR	95% CI
Melanoma	2.21	1.40, 3.49
Prostate	0.96	0.85, 1.07
Testicular	4.59	1.38, 15.27
Bladder	1.04	0.71, 1.54
Kidney	1.11	0.82, 1.49
Brain	0.81	0.36, 1.82

IRRs (HIV-infected vs. HIV-uninfected) for specific cancer types (4)

Cancer	IRR	95% CI
Thyroid	0.62	0.32, 1.20
Hodgkin lymphoma	9.08	5.09, 16.19
NHL	6.68	5.57, 8.00
Multiple myeloma	1.40	0.86, 2.27
Leukemia	2.02	1.33, 3.08
KS	519.61	229.02, 1178.90

Cancer incidence in HIV-infected compared to HIV-uninfected veterans: conclusions

- Overall cancer incidence is about 2-fold higher in HIV-infected than in HIV-uninfected veterans
- PLWHA have elevated ADC incidence
- PLWHA have elevated incidence of a variety of NADC cancer types, many of which have viral etiologies

Cancer risk and prevention in PLWHA

- **Cancer is a major cause of morbidity and mortality in PLWHA**
- **PLWHA have elevated risk for many cancer types, especially those with a viral etiology**, due to
  - HIV infection itself
  - High prevalence of non-HIV cancer risk factors
- Cancer prevention among PLWHA
  - Early ART to preserve/restore immune function
  - Reduction in prevalence of non-HIV cancer risk factors
  - Screening for selected cancer types

Immune system and cancer: a double-edged sword

- Immune system protects against cancer
  - Clears/suppresses oncogenic virus infections
  - Cancer immunosurveillance: recognition and destruction of cancer cells
- Chronic immune activation and inflammation promotes cancer development
  - Stimulation of cell proliferation
  - Generation of genotoxic reactive oxygen and nitrogen species
  - Production of procarcinogenic cytokines and growth factors

Grulich et al. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis

(Lancet 2007;370:59-67)

- Lifestyle-related risk factors probably differ substantially between these 2 groups
- Immunodeficiency is the risk factor these 2 groups have in common
- Similar cancer incidence patterns would suggest immunodeficiency as the cause
- Combined data from population-based cohort studies that compared cancer incidence in the cohort with cancer incidence in the general population

Grulich et al. Meta-analysis

	HIV/AIDS	Transplant
# of studies	7	5
Aggregate cohort size	444,172	31,977 (97% renal)

Cancer types with significant (p<.05) standardized incidence ratios (SIRs) in both HIV and transplant patients, by SIR magnitude

SIR	Cancer types
Both >8	KS (KSHV), non-Hodgkin lymphoma (EBV)
Both >4	Hodgkin lymphoma (EBV), anus (HPV), vulva and vagina (HPV), penis (HPV), non-melanoma skin (HPV)
Both >2	Liver (HCV/HBV), cervix (HPV), oral cavity & pharynx (HPV), lip (HPV), larynx (HPV), eye (HPV), lung, multiple myeloma, leukemia
Both >1.5	Esophagus (HPV), stomach (*H pylori*), kidney
Both >1.2	Melanoma

KSHV, KS-associated herpesvirus; EBV, Epstein-Barr virus;
HPV, human papillomavirus; HCV, hepatitis C virus; HBV, hepatitis B virus

Grulich et al.: conclusions

- Many cancer types had increased incidence in both groups
- Most are of known or suspected viral origin
- Lack of increased incidence of breast and prostate cancers argues against increased medical surveillance as the explanation of increased incidence
- Immunodeficiency is the most likely explanation for the elevated risk

Epidemiologic measures of immune function in HIV infection

- CD4 cell count: measure of immunodeficiency
- HIV viral load (i.e., HIV RNA copies in blood)
  - Rough measure of chronic immune activation and inflammation

CD4 and HIV RNA in relation to KS risk in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)

NA-ACCORD

- Consortium of >20 HIV cohorts
- Validated cancer diagnoses for each cohort by chart review or cancer registry linkage
- Data center standardizes variables among cohorts to create a combined analytic dataset

CD4 and HIV RNA in relation to KS risk in NA-ACCORD

- 15 cohorts
- N = 64,693
- KS cases = 689
- Median follow-up: 6.2 years
- Calculated hazard ratios (HRs) using Cox proportional hazards models
- Models adjusted for age, sex, race/ethnicity, cohort, calendar-period of entry into cohort, HIV risk group, baseline ART

Baseline CD4 in relation to KS risk

CD4 (cells/µl)	HR	95% CI
500+	1.0 (ref)	--
350-499	1.4	1.2-1.7
200-349	1.7	1.3-2.1
100-199	2.1	1.6-2.8
50-99	3.0	2.1-4.3
<50	1.6	1.1-2.4

Time-updated CD4 (6-month lag) in relation to KS risk

CD4 (cells/µl)	HR	95% CI
500+	1.0 (ref)	--
350-499	2.5	1.7-3.7
200-349	5.1	3.6-7.3
100-199	12.2	8.6-17.4
50-99	28.4	19.9-40.7
<50	45.7	32.8-63.7

Baseline HIV RNA in relation to KS risk

HIV RNA (copies/ml)	HR	95% CI
<500	1.0 (ref)	--
500-9,999	1.9	1.2-3.0
10,000-99,999	3.6	2.3-5.5
100,000+	3.5	2.2-5.4

Time-updated HIV RNA (6-month lag) in relation to KS risk

HIV RNA (copies/ml)	HR	95% CI
<500	1.0 (ref)	--
500-9,999	2.7	1.8-4.3
10,000-99,999	11.0	7.5-16.1
100,000+	38.5	28.7-55.6

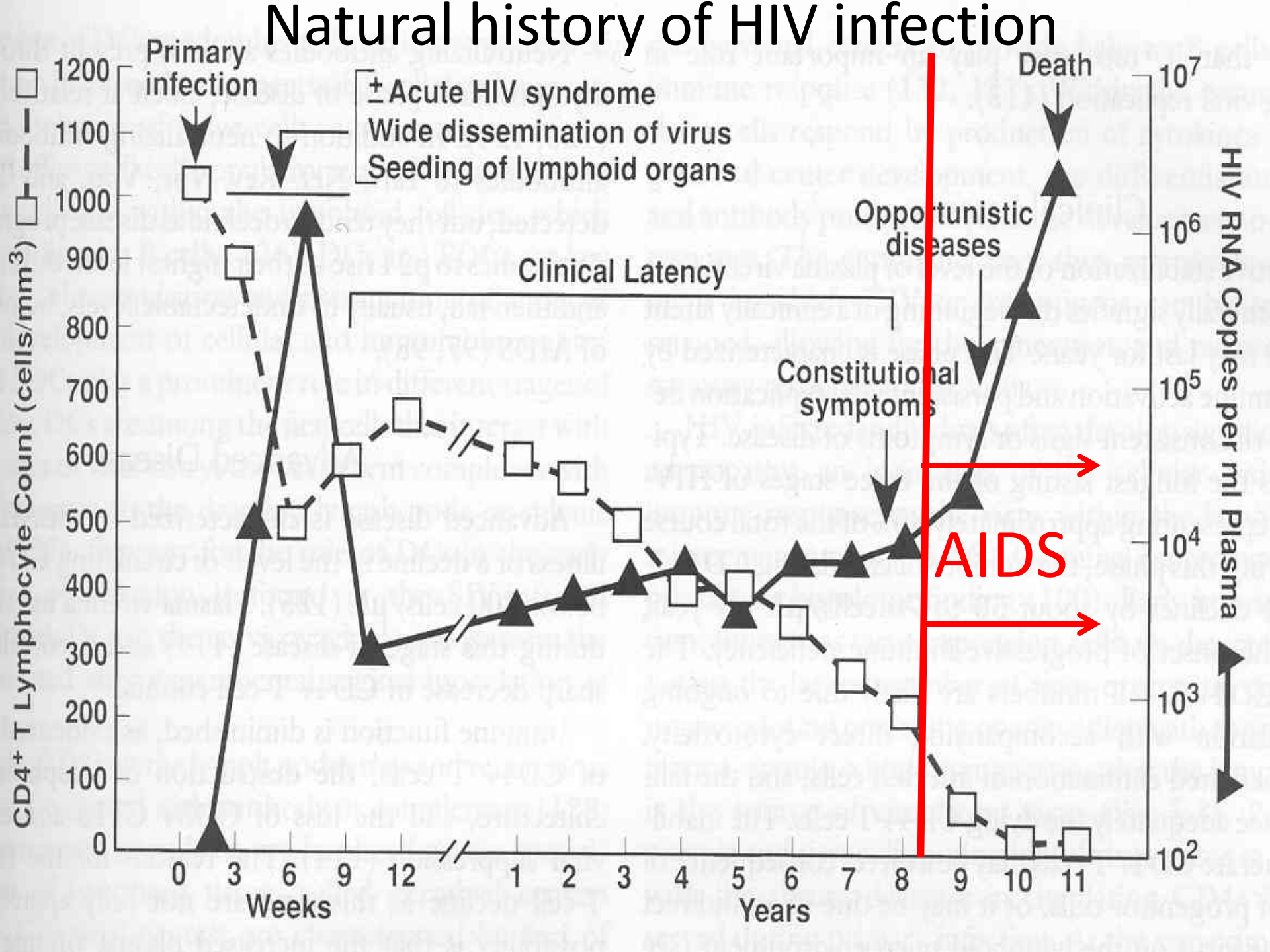
Time-updated CD4 and HIV RNA (6-month lags) (simultaneous adjustment) in relation to KS risk

		HR	95% CI
CD4 (cells/µl)	500+	1.0 (ref)	--
	350-499	2.0	1.4-3.0
	200-349	3.5	2.4-5.0
	100-199	6.8	4.7-9.8
	50-99	13.3	9.1-19.5
	<50	18.7	13.0-27.1
HIV RNA (copies/ml)	<500	1.0 (ref)	--
	500-9,999	1.9	1.2-3.0
	10,000-99,999	5.1	3.4-7.5
	100,000+	9.0	6.0-13.4

CD4 and HIV RNA in relation to KS risk in NA-ACCORD: conclusions

- Time-updated measures of CD4 and HIV RNA must be used to assess these covariates in relation to risk of KS (and of other cancer types)
- Both recent CD4 count and recent HIV RNA level were strong, independent predictors of KS risk

Natural history of HIV infection



HIV infection, immunodeficiency, viral replication, and the risk of cancer

(Silverberg MJ, et al. Cancer Epidemiol Biomarkers Prev 2011;20:2551-9)

- Kaiser Permanente (KP) Northern California cohort
- 20,775 HIV-infected
- 215,158 HIV-uninfected
- Mean observation time
  - HIV-infected: 4.4 years
  - HIV-uninfected: 5.3 years
- Rate ratios from Poisson regression
- Time-updated recent (6-month lag) CD4 and HIV RNA
- Adjusted for age, sex, race/ethnicity, calendar period, KP region, smoking, alcohol/drug abuse, overweight/obesity

Time-updated CD4 and HIV RNA (simultaneous adjustment) in relation to risk of selected NADC

	Adjusted Rate Ratio (95% CI)	
Cancer type	**CD4 (≤200 vs. 500+ cells/µl)**	**HIV RNA (≥10,000 vs. <500 copies/ml)**
Anal	3.1 (1.6-6.1)	0.7 (0.4-1.3)
Hodgkin lymphoma	3.7 (1.8-7.8)	0.9 (0.4-1.8)
Oral cavity/pharynx	5.9 (1.8-19.4)	0.2 (0.0-1.3)
Liver	4.3 (1.2-15.0)	0.4 (0.1-1.5)
Prostate	0.7 (0.3-1.6)	0.5 (0.2-1.1)
Lung	2.0 (0.9-4.1)	0.9 (0.4-1.9)
Colorectal	4.8 (1.9-12.3)	0.5 (0.1-1.4)
Melanoma	1.8 (0.6-6.0)	1.9 (0.8-4.6)

HIV infection, immunodeficiency, viral replication, and the risk of cancer: conclusions

- Low recent CD4 count was associated with increased risk of a variety of NADC after adjustment for HIV RNA, demographic variables, and non-HIV cancer risk factors
- No compelling evidence that high recent HIV RNA was independently associated with increased NADC risk

Cancer risk and prevention in PLWHA

- **Cancer is a major cause of morbidity and mortality in PLWHA**
- **PLWHA have elevated risk for many cancer types, especially those with a viral etiology, due to**
  - **HIV infection itself**
  - High prevalence of non-HIV cancer risk factors
- Cancer prevention among PLWHA
  - Early ART to preserve/restore immune function
  - Reduction in prevalence of non-HIV cancer risk factors
  - Screening for selected cancer types

Modifiable cancer risk factors and associated cancer types

Risk factor	Cancer types
Smoking	Oral cavity/pharynx, esophagus, stomach, pancreas, larynx, lung, cervix, bladder, kidney, acute myeloid leukemia
Alcohol	Oral cavity/pharynx, esophagus, colorectal, liver, larynx, breast
Obesity	Adenocarcinoma of esophagus/gastric cardia, colorectal, pancreas, breast (postmenopausal), endometrial, kidney
HPV	Oral cavity/pharynx, anal, cervix, vagina, vulva, penis
HCV and HBV	Liver

Prevalence of cancer risk factors in PLWHA and general population

Risk factor	General pop.	PLWHA
Current smoking	19%	38%-84%
Hazardous alcohol	3%-32%	11%-20%; IDU: 74%
Obesity	32%-36%	12%-29%
Cervical HPV	27%	44%-79%
Anal HPV	MSM: 57%-70%	59%-98%
Oral HPV	4%-10%	20%-47%
Hepatitis B virus	0.3%	1%-33%
Hepatitis C virus	2%	3%-50%; IDU: 90%

Cancer risk and prevention in PLWHA

- **Cancer is a major cause of morbidity and mortality in PLWHA**
- **PLWHA have elevated risk for many cancer types, especially those with a viral etiology, due to**
  - **HIV infection itself**
  - **High prevalence of non-HIV cancer risk factors**
- Cancer prevention among PLWHA
  - Early ART to preserve/restore immune function
  - Reduction in prevalence of non-HIV cancer risk factors
  - Screening for selected cancer types

Does early ART reduce cancer risk?

- Biologic evidence: effects of ART
  - Suppresses viral load
  - Increases CD4 count
  - Reduces (but does not normalize) immune activation and inflammation
- Increasing evidence from observational epidemiology
- No data available from randomized controlled trials
- Question may be viewed as academic: US Dept. of Health and Human Services guidelines recommend ART for all PLWHA, regardless of CD4 count

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

(Panel on Antiretroviral Guidelines for Adults and Adolescents)

"For those with high CD4 cell counts, whose short-term risk for death may be low, the recommendation to initiate ART is based on growing evidence that untreated HIV infection or uncontrolled viremia is associated with development of non-AIDS-defining diseases, including cardiovascular disease, kidney disease, liver disease, neurologic complications, and malignancies. Furthermore, newer ART regimens are more effective, more convenient, and better tolerated than regimens used in the past."

Reduction in prevalence of non-HIV cancer risk factors

- Targeted interventions needed
- Behavioral and pharmacologic interventions for smoking and alcohol
- Vaccination for HPV, HBV
- Treatment of HBV, HCV

Cancer screening in PLWHA

- Beneficial for patients with sufficient life expectancy
  - Cervical cancer: pap smear
  - Breast cancer: mammography
  - Colorectal cancer: fecal occult blood testing, sigmoidoscopy, colonoscopy
- More research needed to determine benefits vs. harms
  - Anal cancer: cytology, high-resolution anoscopy
  - Lung cancer: low dose CT scan
  - Liver cancer: ultrasonography

Cancer risk and prevention in PLWHA

- Cancer is a major cause of morbidity and mortality in PLWHA
- PLWHA have elevated risk for many cancer types, especially those with a viral etiology, due to
  - HIV infection itself
  - High prevalence of non-HIV cancer risk factors
- Cancer prevention among PLWHA
  - Early ART to preserve/restore immune function
  - Reduction in prevalence of non-HIV cancer risk factors
  - Screening for selected cancer types