SUPPLEMENT

The study population for this analysis included PWH (≥18 years) receiving HIV care in one of 12 clinical cohorts in the North American AIDS Cohort Collaboration on Research and Design or NA-ACCORD (10 in the US and 2 in Canada) who had an incident cancer diagnosis between 1 Jan 2000 and 31 Dec 2009.

In these supplemental analyses, the National Cancer Database (NCDB) was used as comparison group for PWH with and without ADI. The NCDB is a nationwide, facility-based, comprehensive clinical surveillance oncology dataset established in 1989 that collects demographic and oncological patient data from over 1,500 hospital-based cancer registries in the U.S.[20] It is a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons, which has executed a Business Associate Agreement, including data use agreements with accredited hospitals. Cancer cases in the NCDB represent approximately 70% of all incident cancer diagnoses in the U.S. Clinical information including patient age, stage, and survival following diagnosis were ascertained via the NCDB data dictionary.[44]

NCDB participants with a cancer diagnosis between 1 Jan 2000 and 31 Dec 2009 and with complete staging information and follow-up for death were included as the comparison group. Given the low prevalence of HIV in the general population in the U.S. (<1%), the cancer cases in the NCDB were assumed to be from adults without HIV if not already known to have HIV, and therefore, none of them were classified as having an ADI.[45] People with HIV (PWH) have important differences in their risks of cancer as compared to those in the general population, most notably a higher prevalence of smoking, and potentially a greater risk of infections that may be associated with some of the cancer studied.[46,47]

Mortality rates and age-standardized mortality ratios (SMR) were estimated for each cancer type, with the exception of cervical cancer due to an inadequate sample size. The NCDB estimates were calculated by Dr. Grover's group and sent to the NA-ACCORD Epidemiology/Biostatistics Core where SMRs were estimated.

Mortality by HIV Status

Our analysis of PWH diagnosed with anal, lung, cervical, oropharynx cancers or Hodgkin lymphoma demonstrates there is an increased risk of all-cause death amongst PWH with cancer compared to the general population. Prior literature has shown that mortality amongst PWH is 6.9 times higher than mortality of the general population, after excluding deaths from AIDS. This high mortality was factored to be most commonly due to liver disease, drug overdose/addiction, or suicide –and to a lesser extent from non-AIDS defining cancers and cardiovascular disease.[46]

Amongst PWH with cancer, our findings are consistent with prior studies that have found reduced survival amongst PWH diagnosed with cancer.[10,17,48-51] Sigel et al. noted an association of HIV infection and non-small cell lung cancer mortality as well, after

adjusting for SEER summary stage and other competing risks of death.[48] Marcus et al. described reduced survival for lung and prostate cancers PWH that could not be fully explained by stage and other risk factor data collected.[17] A large systematic review on survival after cancer diagnosis among HIV individuals in North America found a higher risk of mortality independent of stage among colorectal, pancreas, larynx, lung, melanoma, breast and prostate cancer cases. However, HIV was not associated with increased cancer mortality for anal, Hodgkin lymphoma or diffuse large B cell lymphoma.[52]

Large population-based studies have shown that independent predictors of poor outcome in PWH with cancer include tumor stage and lack of appropriate cancer treatment. PWH are shown to not receive appropriate cancer therapy due to various reasons, physician bias being one in the modern era and poor performance status and advanced stage in the pre-ART era[52]. Marcus et al. observed less cancer treatment received for PWH with lung cancer[17] and Suneja et al. found treatment disparities between HIV-infected vs. uninfected patients for Hodgkin Lymphoma, lung, prostate, and colorectal cancers[53]. These disparities may be accounted for by provider factors that include believing PWH will not respond to cancer treatment as well or will not be able to tolerate treatment as well as patients without HIV.[17,53,54]

Previous literature has also hypothesized worse outcomes in PWH due to the role of immune suppression. Immune suppression can cause a worsening of cancer biology and cancer treatment tolerability.[55-57] PWH have lower mucosal CD4+ cells, even with increased CD4 cell count on ART. These mucosal cells play an important role in clearance of residual cancerous cells after treatment, and may cause poor response to chemotherapy. Further, PWH may be unable to amount a robust immune response to their cancer causing the cancer to further progress rapidly after diagnosis, especially for cervical and oropharynx cancers.[58,59]

The increase in mortality among PWH with cancer may be due to reduced effectiveness of chemotherapy with ART interactions or noncompliance and discontinuation of ART due to toxicities and side effects of chemotherapy.[60,61] Interactions between ART and chemotherapy drugs mediated by the cyp450 enzyme can occur and are often frequently misunderstood because of the history of exclusion of PWH from chemotherapy clinical trials. These interactions could contribute to the discrepancy in outcomes. However, future research continues to recognize the need for better pharmacokinetic data in patients on ART. [62,63]

Finally, there are potential socio-cultural barriers to receiving equivalent cancer treatment amongst PWH. Large population-based studies note that confounding psychosocial factors, such as co-morbid depression, may act as barriers to access to care for PWH and are an important consideration in explaining potential causes of outcome disparity.[53]

Table S1: Mortality rates and 95% confidence intervals after type-specific cancer diagnoses in the general population (from the National Cancer Database, or NCDB) and people with HIV with and without a history of an AIDS-defining illness at cancer diagnosis, by cancer stage at diagnosis

	General population				No AIDS-defining illness at, or prior to, cancer diagnosis				AIDS-defining illness at, or prior to, cancer diagnosis			
	# of deaths	PY	MR per 100 PY	95% CI	# of deaths	PY	MR per 100 PY	95% CI	# of deaths	PY	MR per 100 PY	95% CI
Anal cancer												
Overall	7,997	81,496.5	9.81	9.60, , 10.03	30	260.5	11.52	8.05 , 16.47	28	152.4	18.37	12.69 , 26.61
Cancer Stage												
I	991	19429.41	5.10	4.79 , 5.43	6	58.6	10.24	4.60 , 22.79	5	44.5	11.24	4.68 , 27.00
II	2934	36572.41	8.02	7.74 , 8.32	12	145.8	8.23	4.67 , 14.49	12	76.3	15.73	8.93 , 27.69
III	2857	22690.21	12.59	12.14 , 13.06	8	46.7	17.13	8.57 , 34.25	8	25.8	31.01	15.51 , 62.00
IV	1215	2804.45	43.32	40.96 , 45.83	4	9.4	42.55	15.97 , 113.38	3	5.8	51.72	16.68 , 160.38
OP												
Overall	4,781	21,391.5	22.35	21.73 , 22.99	45	191.2	23.54	17.57 , 31.52	17	70.2	24.22	15.05 , 38.95
Cancer Stage												
I	379	2,540.1	14.92	13.49 , 16.50	8	52.1	15.36	7.68 , 30.70	1	18.2	5.49	0.77 , 39.01
II	536	3,224.8	16.62	15.27 , 18.09	4	26.8	14.93	5.60 , 39.77	1	24.2	4.13	0.58 , 29.34
III	962	5,084.7	18.92	17.76 , 20.15	3	16.2	18.52	5.97 , 57.42	4	15.2	26.32	9.88 , 70.12
IV	2,904	10,541.9	27.55	26.56 , 28.57	30	96.1	31.22	21.83 , 44.65	11	12.6	87.30	48.35 , 157.64
Hodgkin Lymphoma												
Overall	8,416	182,571.6	4.61	4.51 , 4.71	22	175.4	12.54	8.26 , 19.05	11	65.9	16.69	9.24 , 30.14
Cancer Stage												
I	1169	32103.5	3.64	3.44 , 3.86	4	22.6	17.70	6.64 , 47.16	0	11.1	0.00	--
II	2058	84627.92	2.43	2.33 , 2.54	3	50.3	5.96	1.92 , 18.49	1	19.7	5.08	0.72 , 36.04
III	2440	37290.8	6.54	6.29 , 6.81	4	36.4	10.99	4.12 , 29.28	1	1.1	90.91	12.81 , 645.39
IV	2749	28549.41	9.63	9.28 , 10.00	11	66.1	16.64	9.22 , 30.05	9	34	26.47	13.77 , 50.87

Lung cancer															
Overall	654,818	1,362,643.3	48.05	47.94	,	48.17	186	284.4	65.40	56.65	,	75.51	144	136.7	105.34	89.47	,	124.03
Cancer Stage																		
I	112833	636349.54	17.73	17.63	,	17.84	19	118.4	16.05	10.24	,	25.16	18	57.6	31.25	19.69	,	49.60
II	37640	113966.97	33.03	32.70	,	33.36	10	17.5	57.14	30.75	,	106.20	7	6.9	101.45	48.36	,	212.80
III	187484	336299.03	55.75	55.50	,	56.00	53	89.7	59.09	45.14	,	77.34	43	41.3	104.12	77.22	,	140.39
IV	316861	276027.78	114.79	114.39	,	115.19	104	58.8	176.87	145.94	,	214.35	76	30.9	245.95	196.43	,	307.96

Table S2: AIDS Defining Illnesses (ADIs) prior to or at cancer diagnosis

	Anal cancer		Cervical cancer		Oropharynx cancer		Hodgkin lymphoma		Lung cancer	
	N	%	N	%	N	%	N	%	N	%
AIDS defining diagnosis unspecified	7	10	.	.	.	.	2	8	2	1
Candidiasis	7	10	.	.	1	3	4	15	15	8
Cervical cancer invasive	.	.	5	100	.	.	.	.	.	.
Cytomegalovirus (CMV)	3	4	.	.	1	3	1	4	1	1
Cryptococcosis extrapulmonary, not meningitis	2	3	.	.	3	9	.	.	4	2
HIV encephalopathy (dementia)	2	3	.	.	1	3	2	8	14	8
Histoplasmosis disseminated or extrapulmonary	1	1	.	.	.	.	.	.	3	2
Kaposi sarcoma	4	6	.	.	.	.	.	.	3	2
Non-Hodgkin lymphoma, unspecified	1	1	.	.	.	.	.	.	.	.
Mycobacterium other or unspecified species disseminated or extrapulmonary	5	7	.	.	1	3	3	12	2	1
Tuberculosis (pulmonary, disseminated, or unspecified)	14	18	.	.	9	27	4	15	45	24
Pneumocystis jiroveci pneumonia (PCP)	18	25	.	.	7	21	6	23	35	19
Pneumonia (or recurrent Pneumonia)	5	7	.	.	4	12	1	4	45	24
Wasting syndrome due to HIV	.	.	.	.	6	18	2	8	12	6
Other*	2	3	.	.	.	.	1	4	4	2
Total	71	100	5	100	33	100	26	100	186	100

*Others (n≤2 per each diagnosis): Cryptococcal meningitis, Cryptosporidiosis chronic, intestinal; Progressive multifocal leukoencepholopathy (PML); Isosporiasis chronic intestinal; Mycobacterium avium complex (MAC) or M. kanasaii disseminated or extrapulmonary; Toxoplasmosis of the brain.

Figure S1: Standardized mortality rate ratios comparing adults with HIV in the NA-ACCORD to adults without HIV in the National Cancer Database