

Article

Trends in Cancer Incidence in Different Antiretroviral Treatment-Eras amongst People with HIV

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Simple Summary: Cancer is a leading cause of death, both in the general population and in people with HIV. We aimed to assess temporal trends of cancer from 2006 to 2021 in two international HIV cohort collaborations (D:A:D and RESPOND). We assessed overall cancer, AIDS-defining cancers (ADCs), non-ADCs (NADCs), infection-related cancers, body mass index (BMI)-related cancers, and

smoking-related cancers. Amongst almost 65,000 individuals, we found that the age-standardised incidence of all cancers remained fairly constant over time; however, the incidence of ADCs and infection-related cancers both decreased, whilst the incidence of NADCs, smoking-related cancers, and BMI-related cancers increased. Trends were similar after adjusting for demographics, comorbidities, and HIV-related factors. Our results highlight the need for better prevention strategies to reduce the incidence of NADCs, smoking-related cancers, and BMI-related cancers.

Abstract: Despite cancer being a leading comorbidity amongst individuals with HIV, there are limited data assessing cancer trends across different antiretroviral therapy (ART)-eras. We calculated age-standardised cancer incidence rates (IRs) from 2006–2021 in two international cohort collaborations (D:A:D and RESPOND). Poisson regression was used to assess temporal trends, adjusted for potential confounders. Amongst 64,937 individuals (31% ART-naïve at baseline) and 490,376 total person-years of follow-up (PYFU), there were 3763 incident cancers (IR 7.7/1000 PYFU [95% CI 7.4, 7.9]): 950 AIDS-defining cancers (ADCs), 2813 non-ADCs, 1677 infection-related cancers, 1372 smoking-related cancers, and 719 BMI-related cancers (groups were not mutually exclusive). Age-standardised IRs for overall cancer remained fairly constant over time (8.22/1000 PYFU [7.52, 8.97] in 2006–2007, 7.54 [6.59, 8.59] in 2020–2021). The incidence of ADCs (3.23 [2.79, 3.72], 0.99 [0.67, 1.42]) and infection-related cancers (4.83 [4.2, 5.41], 2.43 [1.90, 3.05]) decreased over time, whilst the incidence of non-ADCs (4.99 [4.44, 5.58], 6.55 [5.67, 7.53]), smoking-related cancers (2.38 [2.01, 2.79], 3.25 [2.63–3.96]), and BMI-related cancers (1.07 [0.83, 1.37], 1.88 [1.42, 2.44]) increased. Trends were similar after adjusting for demographics, comorbidities, HIV-related factors, and ART use. These results highlight the need for better prevention strategies to reduce the incidence of NADCs, smoking-, and BMI-related cancers.

Keywords: HIV; non-AIDS defining cancer; AIDS defining cancer; incidence; trends; smoking; infection; body mass index

1. Introduction

Cancer is a leading cause of death, both in the general population and in people with HIV, in industrialised countries [1–5]. Previous studies have shown that the incidence of AIDS-defining cancers (ADCs; defined as non-Hodgkin’s lymphoma, Kaposi’s sarcoma, and cervical cancer), as well as several non-ADCs (NADCs), such as anal cancer and Hodgkin’s lymphoma, is higher amongst people with HIV compared to the general HIV-indeterminate population, partially due to the impact of HIV-induced immunosuppression [6–8].

Since the introduction of combination antiretroviral therapy (ART), there has been improved survival for people with HIV, and increases in the CD4 count have led to a drastic reduction in the incidence of ADCs [9–14]. In contrast, a previous study in the Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) collaboration showed that the incidence of NADCs remained stable from 2004 to 2010 amongst 41,746 individuals from across Europe, Australia, and the United States [15], with other studies showing an increase in the incidence of NADCs, although generally only based on follow-up until 2012 [2,13,16]. The reasons for changes in the incidence of NADCs are likely to be multifaceted. An increased risk is likely attributable, at least in part, to the aging of the population as a result of an increased life expectancy of people with HIV [8,17–20]. Additionally, the prevalence of risk factors for cancer, such as smoking, substance use, and alcohol use, remains relatively high amongst some subgroups with HIV [21].

Whilst effective ART reduces the risk of ADCs, it may also reduce the risk of some NADCs through reducing HIV-associated immune dysfunction and persistent inflammation [12–14,22]. Earlier initiation of ART may further contribute to the reduction in the risk of some NADCs [23]. On the other hand, whilst ART is effective at improving immune function and maintaining HIV viral load (VL) suppression, it is a lifelong commitment, and

there are potential long-term toxicities associated with some antiretrovirals (ARVs) [24]. Previous studies have suggested that use of first-generation protease inhibitors (PIs), for example, may be associated with an increased risk of anal cancer [25–27], although recent studies have found conflicting results [28]. This has not been shown for newer ARVs, albeit analyses are limited to relatively short follow-up times; more recently, a previous study in the International Cohort Consortium of Infectious Diseases (RESPOND) collaboration showed that increasing exposure to integrase inhibitors (INSTIs) was not associated with an increased risk of NADCs, although again, this may have been limited by a relatively short follow-up time on INSTIs [29].

As lifestyle factors, the use of cancer preventative measures and ART use have changed over time; it is possible that cancer trends differ among different types of cancers, for example, cancers related to body mass index (BMI), to smoking, or to infection. Our aim was to assess changes in the incidence of both overall cancer and different types of cancer, including ADCs, NADCs, infection-related cancers, BMI-related cancers, and smoking-related cancers, from 2006 to 2021 in the D:A:D and the RESPOND international cohort collaborations.

2. Materials and Methods

2.1. Study Design

This analysis combined data from the D:A:D and RESPOND cohort collaborations. D:A:D and RESPOND are prospective, multi-cohort collaborations from across Europe and Australia, including 11 cohorts and approximately 49,000 individuals with HIV in D:A:D, and 17 cohorts and approximately 35,000 individuals in RESPOND. D:A:D was initiated in 1999 and ran until 2016; RESPOND was initiated in 2017 and is ongoing. Several cohorts contributed data to both D:A:D and RESPOND, and a subset of individuals was included in both collaborations (i.e., they contributed data to both D:A:D and RESPOND). Further details on each study have been published elsewhere [30,31].

D:A:D and RESPOND use the same underlying methodology and collect similar data. In both collaborations, clinical and demographic data are collected on individuals during routine clinical care. Data are reported at the time of enrolment into the collaboration and prospectively annually thereafter. Data in RESPOND are also collected on the 5 years prior to enrolment, and earlier if available. Data on clinical events, including cancers, are collected in real time. Clinical events occurring during the study's validation period (in D:A:D: 2004 onwards; in RESPOND: 12 months prior to the last local cohort visit before RESPOND enrolment onwards) are reported using a study-specific case report form. These events are centrally validated by a clinician at the study coordinating centre using a prespecified algorithm [32,33]. Any missing information is queried, and a selection of all cancer events are externally reviewed further by an oncologist.

2.2. Participants

Individuals from RESPOND and D:A:D were included in this analysis if they were aged 18 years or older at baseline, as defined below, and had any follow-up data. Additionally, individuals from RESPOND were excluded if they did not have a CD4 count and VL measurement either 1 year prior to or within 12 weeks after baseline, or if they had missing information on gender ($n = 7$). These exclusion criteria were not applied to individuals from D:A:D for consistency with previous D:A:D analyses; however, a sensitivity analysis was performed, applying the same exclusion criteria to individuals from D:A:D.

For participants in D:A:D, baseline was defined as the latest of the date of entry into D:A:D and 1 January 2006 [23]. For RESPOND, baseline was defined as the latest of the local cohort enrolment and 1 January 2012.

2.3. Outcome Definitions

The primary outcome was any incident cancer during follow-up. Pre-cancers, basal or squamous cell skin cancers, and a relapse of or metastases from a primary cancer are not

systematically collected and are, therefore, excluded. The definition of cancers is the same in D:A:D and RESPOND; further detail is provided in the RESPOND and D:A:D manual of operations [32,33]. For individuals who had cancer prior to baseline, cancer during follow-up was only counted if the type of cancer was different from the one occurring prior to baseline (e.g., liver cancer prior to baseline followed by anal cancer after baseline). If the type of cancer prior to baseline was unknown, no cancers during follow-up were included. A sensitivity analysis was performed, excluding individuals with any cancer prior to baseline.

Individuals in D:A:D were followed until the earliest of first cancer event, 6 months after last clinic visit, or 1 February 2016 (D:A:D end date) [34]. Individuals in RESPOND were followed until the earliest of the first cancer event, final follow-up, or 31 December 2021 (RESPOND censoring date), with final follow-up defined as the latest of the most recent CD4 count, VL measurement, ART start date, drop out date, or date of death. Individuals who were included in both D:A:D and RESPOND were followed until the latest of the final follow-up in D:A:D or the final follow-up in RESPOND. Data for these individuals were merged (i.e., any repeated data from the overlapping time period between D:A:D and RESPOND was deleted), and for individuals with conflicting data in the two collaborations, data were used from D:A:D until the date of the RESPOND baseline, and data from RESPOND were used thereafter, unless there was a clear error in one of the studies or data were missing from one study and not the other.

Cancers were split into ADCs and NADCs, and were separately categorised into infection-related cancers (including all ADCs), smoking-related cancers, and BMI-related cancers. Cancers included in each category are shown in Supplementary Tables S1 and S2. These categories were developed by a cancer working group including external oncologists [24]. Each cancer type could be included in more than one category, if appropriate, and therefore, the groups are not mutually exclusive. BMI-related cancers were included irrespective of an individual's BMI history or BMI at the time of diagnosis, and similarly, smoking-related cancers were included irrespective of an individual's smoking status.

2.4. Statistical Methods

Baseline characteristics of all participants included in the analysis were summarised and compared between those who went on to develop an incident cancer during follow-up and those who did not.

The crude incidence and age-standardised incidence of any cancer and each cancer subtype was estimated for the following time periods: 2006–2007, 2008–2009, 2010–2011, 2012–2013, 2014–2015, 2016–2017, 2018–2019, and 2020–2021. Incidence rates (IRs) were standardised according to the age distribution of the combined D:A:D and RESPOND cohorts in 2015 [35,36]. Confidence intervals (CIs) for standardised incidence rates were calculated using Dobson's method [37].

Poisson regression with robust standard errors was used to assess the association between cancer incidence and calendar year of follow-up, adjusted for potential confounders (as defined in Table 1 footnote), chosen a priori. These included age (per 1 year increase), gender, ethnicity, geographical region, HIV acquisition group, nadir and baseline CD4 count, ART-experienced and viral suppression status, and whether individuals had a prior ADC or NADC, all defined at baseline. Additionally, models were adjusted for BMI, smoking status, and whether individuals had HCV, HBV, hypertension, diabetes, dyslipidaemia, a prior non-cancer AIDS event, end-stage liver and renal disease, cardiovascular disease, or chronic kidney disease, as well as any exposure to INSTIs, PIs, nucleos/tide reverse transcriptase inhibitors (NRTIs), and non-NRTIs (NNRTIs). These variables were all fitted as time updated. CD4 count and viral suppression was fixed at baseline, as it was likely collinear with other time-updated variables included in the model, such as AIDS events. As prior ART-experienced and viral suppression status at baseline was correlated with exposure to the different ARV drug classes, the primary model only included the baseline ART-experienced and viral suppression status. Then, in a sensitivity analysis,

ART-experienced at baseline was not included, but time-updated exposure to PIs, INSTIs, NRTIs, and NNRTIs, and baseline VL was included. Models were run separately for all cancers as a composite outcome and then for each subcategory of cancer.

Table 1. Baseline characteristics, overall and split by those who had cancer during follow-up and those who did not.

		Overall (n = 64,937)		Cancer during Follow-Up (n = 3763)		No Cancer during Follow-Up (n = 61,174)	
		n	(%)	n	(%)	n	(%)
Gender [§]	Male	48,208	(74.2)	3001	(79.8)	45,207	(73.9)
	Female	16,674	(25.7)	761	(20.2)	15,913	(26.0)
	Transgender	51	(0.1)	1	(0.0)	50	(0.1)
Ethnicity	White	36,711	(56.5)	2188	(58.1)	34,523	(56.4)
	Black	6279	(9.7)	173	(4.6)	6106	(10.0)
	Other	2299	(3.5)	62	(1.6)	2237	(3.7)
	Unknown	19,648	(30.3)	1340	(35.6)	18,308	(29.9)
Body Mass Index (kg/m ²)	<18.5	2636	(4.1)	209	(5.6)	2427	(4.0)
	18.5–<25	31,838	(49.0)	1954	(51.9)	29,884	(48.9)
	25–<30	3323	(5.1)	165	(4.4)	3158	(5.2)
	30+	12,402	(19.1)	770	(20.5)	11,632	(19.0)
	Unknown	14,738	(22.7)	665	(17.7)	14,073	(23.0)
Geographical Region ^a	Western Europe	25,415	(39.1)	1626	(43.2)	23,789	(38.9)
	Southern Europe	11,630	(18.8)	684	(18.2)	10,946	(17.9)
	Northern Europe	20,429	(31.4)	1286	(34.1)	19,143	(31.3)
	Eastern Europe	6011	(9.3)	167	(4.4)	5844	(9.6)
	USA	1452	(2.2)	0	(0.0)	1452	(2.4)
Mode of HIV Acquisition	MSM	29,410	(45.3)	1820	(48.4)	27,590	(45.1)
	IDU	8721	(13.4)	589	(15.7)	8132	(13.3)
	Heterosexual	22,290	(34.3)	1103	(29.3)	21,187	(34.6)
	Other	1380	(2.1)	83	(2.2)	1297	(2.1)
	Unknown	3136	(4.8)	168	(4.5)	2968	(4.9)
Smoking Status	Never	16,340	(25.2)	809	(21.5)	15,531	(25.4)
	Current	23,836	(36.7)	1630	(43.3)	22,206	(36.3)
	Previous	9874	(15.2)	697	(18.5)	9177	(15.0)
	Unknown	14,887	(22.9)	627	(16.7)	14,260	(23.3)
ART treatment history status	Naïve	20,118	(31.0)	990	(26.3)	19,128	(31.3)
	Experienced, VL < 200 cps/mL	34,289	(52.8)	2040	(54.2)	32,249	(52.7)
	Experienced, VL ≥ 200 cps/mL	9062	(14.0)	652	(17.3)	8410	(13.7)
	Experienced, unknown VL	1468	(2.3)	81	(2.2)	1387	(2.3)
Prior exposure to INSTIs		1399	(2.2)	41	(1.1)	1358	(2.2)
Prior exposure to PIs		30,693	(47.3)	2150	(57.1)	28,543	(46.7)
Prior exposure to NNRTIs		30,478	(46.9)	1919	(51.0)	28,559	(46.7)
Prior exposure to NRTIs		25,788	(39.7)	1900	(50.5)	23,888	(39.1)
Prior AIDS	No	51,896	(79.9)	2735	(72.7)	49,161	(80.4)
	Yes	13,041	(20.1)	1028	(27.3)	12,013	(19.6)
Hepatitis C ^b	No	42,872	(66.0)	2528	(67.2)	40,344	(65.9)
	Yes	12,449	(19.2)	806	(21.4)	11,643	(19.0)
	Unknown	9616	(14.8)	429	(11.4)	9187	(15.0)
Hepatitis B ^c	No	52,794	(81.3)	3157	(83.9)	49,637	(81.1)
	Yes	2703	(4.2)	206	(5.5)	2497	(4.1)
	Unknown	9440	(14.5)	400	(10.6)	9040	(14.8)
Hypertension ^d	No	51,164	(78.8)	2765	(73.5)	48,399	(79.1)
	Yes	9632	(14.8)	859	(22.8)	8773	(14.3)
	Unknown	4141	(6.4)	139	(3.7)	4002	(6.5)
Diabetes ^e	No	63,054	(97.1)	3561	(94.6)	59,493	(97.3)
	Yes	1883	(2.9)	202	(5.4)	1681	(2.7)
Prior Cancer	No	61,053	(94.0)	3438	(91.4)	57,615	(94.2)
	Yes	3122	(4.8)	302	(8.0)	2820	(4.6)
	Unknown	762	(1.2)	23	(0.6)	739	(1.2)

Table 1. Cont.

		Overall (<i>n</i> = 64,937)		Cancer during Follow-Up (<i>n</i> = 3763)		No Cancer during Follow-Up (<i>n</i> = 61,174)	
		<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)
Dyslipidaemia ^f	No	25,705	(39.6)	1085	(28.8)	24,620	(40.2)
	Yes	39,232	(60.4)	2678	(71.2)	36,554	(59.8)
Continuous variables		Median	(IQR)	Median	(IQR)	Median	(IQR)
Baseline date, month/year		09/06	(01/06, 01/12)	01/06	(01/06, 11/08)	12/06	(01/06, 01/12)
Age, years		42	(35, 49)	48	(41, 56)	42	(35, 49)
CD4 cell nadir, cells/mm ³ ^g		244	(116, 400)	194	(77, 333)	248	(120, 401)
CD4 at baseline, cells/mm ³ ^g		470	(312, 661)	432	(263, 635)	472	(315, 663)
VL at baseline, copies/mL		50	(49, 12400)	50	(49, 18986)	50	(46, 12100)
Total duration of previous ART for those who started ART, years		6.5	(2.5, 9.9)	8.6	(4.5, 11.8)	6.4	(2.5, 9.7)

Abbreviations: MSM—men who have sex with men; IDU—intravenous drug user; ART—antiretroviral therapy; VL—viral load; cps—copies; INSTIs—integrase inhibitors, PIs—protease inhibitors; NRTIs—nucleoside reverse transcriptase inhibitors; NNRTIs—non-NRTIs; IQR—interquartile range; ^g Transgender was not collected in D:A:D; ^a Due to small numbers, Australia was combined with Northern Europe, and Eastern Central Europe combined with Eastern Europe. ^b Hepatitis C (HCV) was defined by use of anti-HCV medication, a positive HCV antibody test, a positive HCV RNA qualitative test, HCV RNA-VL > 615 IU/mL, and/or a positive genotype test [38]. ^c Hepatitis B (HBV) was defined by a positive HBV surface antigen and/or HBV DNA-VL > 357 IU/mL. ^d Hypertension was confirmed by use of anti-hypertensives at any time before baseline, or if the most recent systolic or diastolic blood pressure measurement before baseline was higher than 140 or 90 mmHg, respectively. ^e Diabetes was defined by a reported diagnosis, use of anti-diabetic medication, glucose \geq 11.1 mmol/L, and/or HbA1c \geq 6.5% or \geq 48 mmol/mol. ^f Dyslipidaemia was defined as total cholesterol > 239.4 mg/dL or HDL cholesterol < 34.7 mg/dL or triglyceride >203.55 mg/dL or use of lipid-lowering treatments [39]. ^g CD4 count was taken as the most recent measurements in the 12 months prior to baseline. If no measurements were taken prior to baseline, the first measurement within 12 weeks after baseline was used, and CD4 cell nadir was recorded as the same as CD4 count at baseline. Less than 5% of individuals had prior cardiovascular disease, chronic kidney disease, or end-stage liver disease at baseline.

2.4.1. Subgroup Analysis

Several subgroup analyses, defined a priori, were performed to assess whether cancer trends over time differed according to gender, ethnicity, baseline age, HIV acquisition group, geographical region, baseline ART exposure and viral suppression status, CD4 nadir, baseline immunosuppression status (defined as a CD4 count below 350 cells/mm³), or whether individuals had chronic HBV, HCV, or a prior AIDS event at baseline. These were conducted by including an interaction term between the time period and the subgroup of interest in Poisson regression models, adjusted for age.

2.4.2. Missing Data

In all analyses, missing data for categorical variables were accounted for by including an unknown category in the regression models. The analysis was then repeated using complete case analysis, where individuals with missing data for any variables included in the multivariable Poisson regression model, as listed above, were excluded.

Analyses were performed using Stata/SE 17.0 (StataCorp LLC, College Station, TX, USA). *P*-values reported are two-sided, with a *p*-value <0.05 defined as statistically significant.

3. Results

In total, 64,937 participants were included in the analysis (Figure 1). Of these, 31,348 (48.3%) individuals were from D:A:D only, 23,970 (36.9%) were from RESPOND only, and 9619 (14.8%) were recruited into both cohorts.

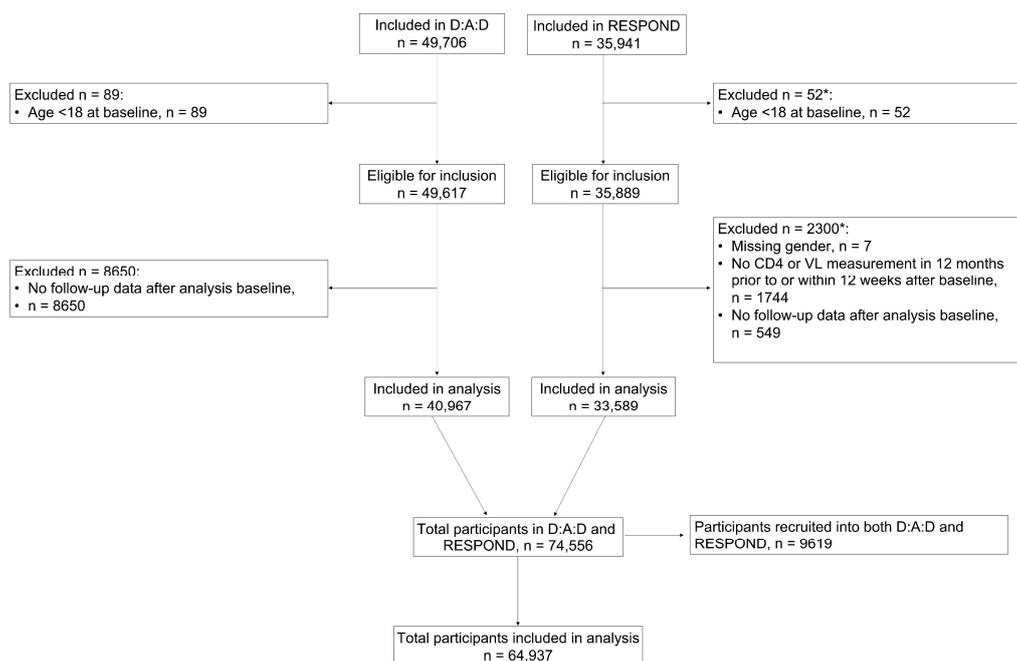


Figure 1. Participant flow for the analysis. * More than one reason could reply. Note, 9619 participants recruited into both D:A:D and RESPOND were only included once in the analysis dataset, with their data from D:A:D and RESPOND merged.

3.1. Baseline Characteristics

Of those included in the analysis, 74% were male, with a median baseline age of 42 years (interquartile range, IQR, 35, 49; Table 1), and approximately half of individuals were either current or previous smokers at baseline (25% never smokers, 37% current smokers, 15% previous smokers, 23% unknown).

In total, 3763 (5.8%) individuals developed at least 1 cancer during follow-up, and when comparing baseline characteristics between participants who developed a cancer during follow-up and those who did not, those with cancer were older at baseline (median age 48 [41, 56] years for those with cancer vs. 42 [35, 49] years for those without cancer; $p < 0.0001$) and had a lower median CD4 count (432 cells/mm³ [263, 635] vs. 472 [315, 663], $p < 0.0001$). Additionally, a higher proportion were current and previous smokers (43% current smokers and 19% previous smokers vs. 36% current smokers and 15% previous smokers; $p < 0.0001$), and a higher proportion had prior cancer (8% vs. 5%; $p < 0.0001$).

3.2. Cancer Trends

Median follow-up for participants was 8.4 years (IQR 4.5, 10.0; total PYFU 490,376), and the incidence of cancer during follow-up was 7.67/1000 PYFU (95% CI: 7.43, 7.92). In total, 950 individuals developed an ADC (IR 1.94/1000 PYFU [1.82, 2.07]) and 2813 an NADC (IR 5.73 [5.53, 5.95]). There were 1677 infection-related cancers (IR 3.42 [3.26, 3.59]), 1372 smoking-related cancers (2.80 [2.66, 2.95]), and 719 BMI-related cancers (1.47 [1.36, 1.58]). The most common cancers were non-Hodgkin's lymphoma ($n = 447$), Kaposi's sarcoma ($n = 423$), lung cancer ($n = 390$), anal cancer ($n = 284$), and prostate cancer ($n = 248$). These cancers were consistently the most common cancers across the time periods from 2006 to 2021. Supplementary Tables S1 and S2 show the number of each cancer reported, by cancer subtype.

Between 2006 and 2021, the age-standardised incidence of all cancers remained fairly constant over time (8.22/1000 PYFU [7.52, 8.97] in 2006–2007, 7.54 [6.59, 8.59] in 2020–2021; Figure 2). Over the same time period, the incidence of ADCs decreased substantially (3.23 [2.79, 3.72] in 2006–2007, 0.99 [0.67, 1.42] in 2020–2021) as did the incidence of infection-related cancers (4.83 [4.29, 5.41] in 2006–2007, 2.43 [1.90, 3.05] in 2020–2021). As can be seen

in Figure 2, the rate of decrease for both cancer types was faster pre-2012, after which the incidence continued to decrease, but at a slower rate. Conversely, the incidence of NADCs increased over time (4.99 [4.44, 5.58] in 2006–2007, 6.55 [5.67, 7.53] in 2020–2021), although the rate of increase appeared to be slowing in more recent time periods from 2018–2021, as can be seen in Figure 2. Similarly, smoking-related cancers (2.38 [2.01, 2.79] in 2006–2007, 3.25 [2.63, 3.96] in 2020–2021) and BMI-related cancers (1.07 [0.83, 1.37] in 2006–2007, 1.88 [1.42, 2.44] in 2020–2021) increased over time. As liver cancer ($n = 192$) was a common contributor to all cancer categories, apart from ADCs, this was removed from all categories, and the analyses were rerun, with similar results found (Supplementary Figure S1).

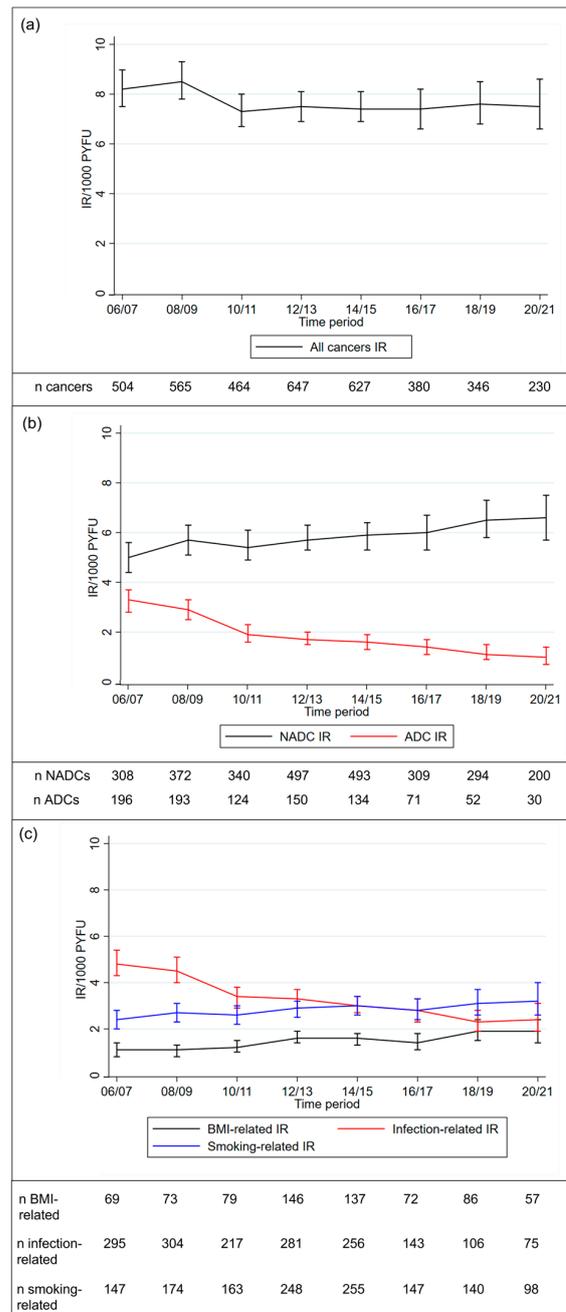


Figure 2. Age-standardised incidence rates and 95% confidence intervals over time for (a) all cancers; (b) ADCs and NADCs; (c) infection-related, smoking-related, and BMI-related cancers. Abbreviations: ADC—AIDS-defining cancer; NADC—non-AIDS-defining cancer; IR—incidence rate.

The CD4 count at time of cancer diagnosis was also assessed. Of the 3763 individuals with a cancer during follow-up, 94% had a CD4 measurement within 1 year prior to the diagnosis (median [IQR] time from CD4 measurement to cancer diagnosis 50 days [17, 102]). The median CD4 count was 478 cells/mm³ (IQR 288, 688) for all cancers, 524 cells/mm³ (347, 739) for NADCs, 320 cells/mm³ (161, 520) for ADCs, and 378 cells/mm³ (203, 580) for infection-related cancers. The CD4 count at the time of diagnosis increased over time for all cancers (360 cells/mm³ [206, 546] in 2006–07, 612 cells/mm³ [402, 839] in 2020–21) and NADCs (399 cells/mm³ [249, 589], 637 cells/mm³ [447, 855]), as shown in Supplementary Figure S2, as well as for infection-related cancers (291 cells/mm³ [160, 447], 514 cells/mm³ [221, 858]). However, for ADCs, the median CD4 count stayed fairly constant over time (280 cells/mm³ [139, 440], 264 cells/mm³ [112, 688]).

Poisson regression models were used to assess cancer temporal trends, after adjusting for demographic, clinical, HIV, and ART-related factors (Figure 3, Supplementary Tables S3 and S4). In these models, the time period was fitted as a categorical variable. The results showed that the adjusted incidence of overall cancer did not change significantly over time (compared to 2006–2007: 2020–2021 adjusted IR ratio 1.00 [95% CI 0.84, 1.18], global $p = 0.41$). As for the age-standardised rates, the incidence of ADCs (0.29 [0.19, 0.45], $p < 0.0001$) and infection-related cancers (0.52 [0.40, 0.69], $p < 0.0001$) decreased over time, whilst the incidence of NADCs (1.55 [1.28, 1.89], $p < 0.0001$), smoking-related cancers (1.71 [1.29, 2.26], $p = 0.0005$), and BMI-related cancers (1.80 [1.23, 2.64], $p = 0.0001$) increased over time.

After adjusting for time-updated exposure to different ARV drug classes (INSTIs, PIs, NNRTIs, and NRTIs), the incidence of ADCs (compared to 2006–2007: 2020–2021 adjusted IR ratio 0.73 [0.46, 1.16], global $p = 0.40$) and infection-related cancers (0.86 [0.64, 1.16], $p = 0.51$) decreased over time, although this was no longer significant, suggesting that exposure to ART is likely causing the decreasing incidence of ADCs and infection-related cancers (Supplementary Table S3). There was also a slight increase in all cancers over time, although, again, this was not significant (2020–2021: 1.26 [1.04, 1.52], global $p = 0.18$). The incidence of NADCs (1.55 [1.26, 1.92], global $p = 0.0001$), smoking-related cancers (1.72 [1.28, 2.31], $p = 0.002$), and BMI-related cancers (1.63 [1.10, 2.44], $p = 0.0018$) increased over time, as in the previous model.

The results were consistent across a range of sensitivity analyses, including when fixing all potential confounders at baseline, when excluding individuals with any cancer prior to baseline, and when only including events that occurred during the study validation period (as defined in the methods above), and were centrally validated (Supplementary Table S3). Further, the results were consistent when applying the same exclusion criteria in RESPOND to D:A:D participants and when using complete case analysis to account for missing data.

3.3. Subgroup Analyses

There was a significant interaction between ART-experienced at baseline and the time-period ($p < 0.0001$), likely primarily driven by ADCs (Figure 4). Whilst the incidence of all cancers decreased over time in individuals who were ART-naïve ($n = 20,118$) or ART-experienced with uncontrolled viremia ($n = 9062$) at baseline, it slightly increased for those who were ART-experienced with a suppressed VL ($n = 34,289$), as shown in Figure 4. For all other subgroup analyses, the p value for the test of interaction was >0.1 .

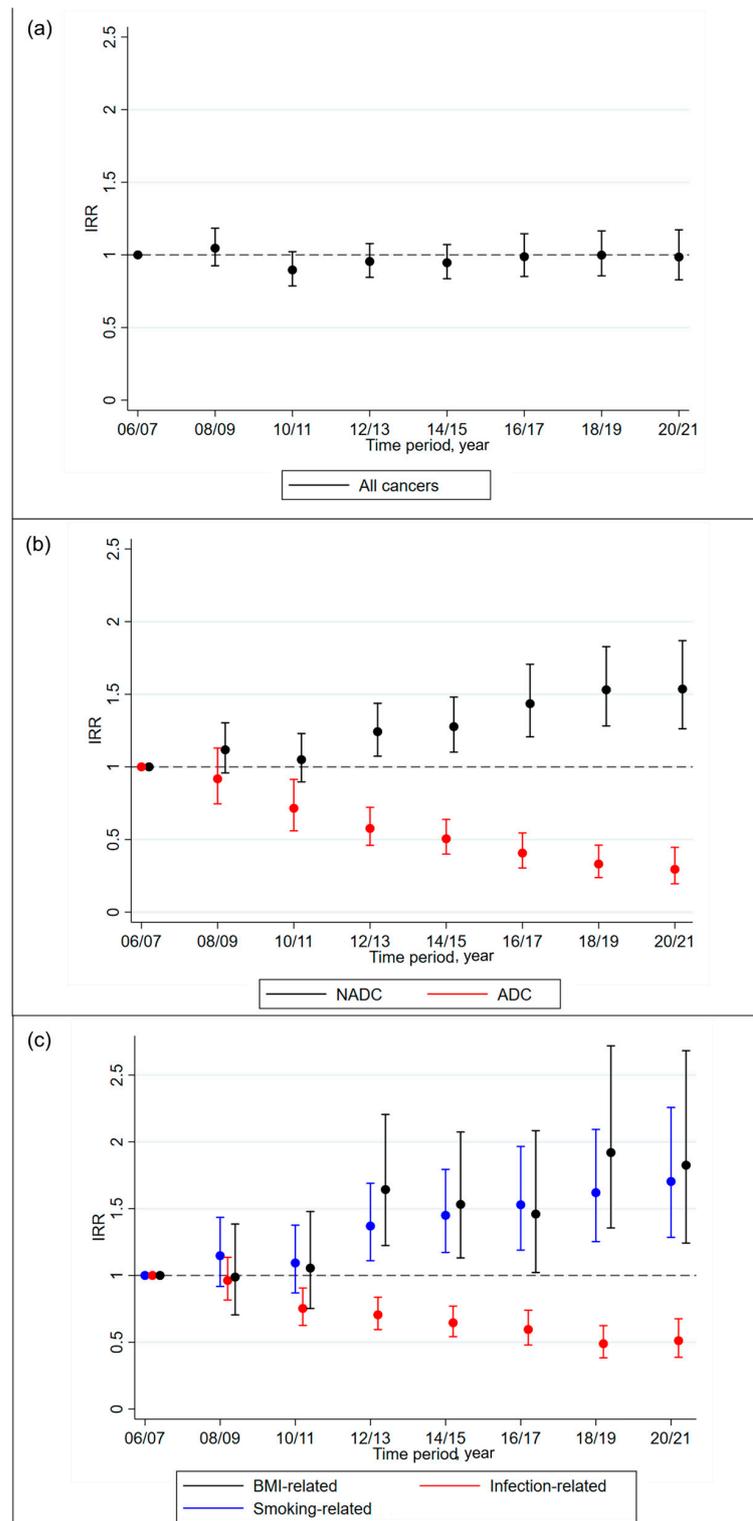


Figure 3. Change in incidence over time, after adjusting for potential confounders for (a) all cancers; (b) ADCs and NADCs; (c) infection-related, smoking-related, and BMI-related cancers. Abbreviations: ADC—AIDS-defining cancer; NADC—non-AIDS-defining cancer; IRR—incidence rate ratio. IRR calculated from a Poisson regression model adjusted for age, gender, ethnicity, CD4 count, CD4 nadir, prior cancer, and ART-experienced and viral suppression status, all fixed at baseline, and smoking status, body mass index, hepatitis C, hepatitis B, hypertension, diabetes, AIDS event, cardiovascular disease, end-stage liver disease, and end-stage renal disease, all time updated.

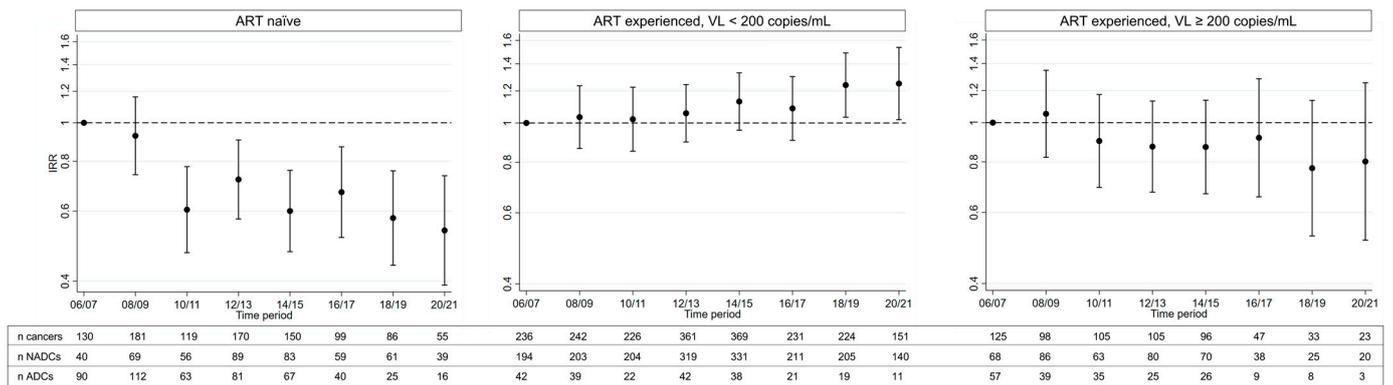


Figure 4. Change in the age-adjusted incidence of all cancers, by time period compared to 2006–2007, stratified by ART-experienced at baseline. IRR calculated from a Poisson regression model, adjusted for age and including an interaction term between the time period and ART-experienced at baseline.

4. Discussion

This is the first analysis to combine data from the D:A:D and RESPOND cohort collaborations, allowing for the assessment of temporal cancer trends over 15 years in large, international settings. Whilst many studies have compared the incidence of ADCs and NADCs before and after the introduction of ART [17,18,21,40], few have compared temporal trends in recent years, when more contemporary ARVs have become available. Amongst 64,937 people with HIV, contributing almost 500,000 PYFU, we found that after accounting for the fact that the population was aging over time, the incidence of all cancers remained fairly constant from 2006 to 2021. However, this trend differed markedly between different cancer types, and whilst ADCs and infection-related cancers have both decreased over time, NADCs, smoking-related cancers, and BMI-related cancers increased.

In this analysis, the incidence was 7.67/1000 PYFU for all cancers, 1.94/1000 PYFU for ADC, and 5.73/1000 PYFU for NADC. Cancer incidence estimates vary substantially across studies including people with HIV, with some studies reporting higher incidence rates [40,41], and others reporting similar [15,18] or lower rates [9,11,17] than those presented here. These variations are likely caused by differences among the studies in terms of the study design, event definition, and time period assessed. For example, several of the studies with higher incidence rates began follow-up in the 1980s, when the incidence of ADCs was considerably higher. An earlier analysis performed on the D:A:D data with follow-up up to 2010 reported a lower incidence of NADCs of 5.0/1000 PYFU, but a higher incidence of ADCs of 3.5/1000 PYFU [15]. This is likely due to the fact that our analysis included a later follow-up, with a higher proportion of individuals on ART, and a slightly older median age. Again, a higher incidence of ADCs was found in a study from NA-ACCORD, which reported an incidence of 2.8/1000 PYFU, although only including Kaposi’s sarcoma and non-Hodgkin’s lymphoma [8], and a study from Kaiser Permanente, which reported an incidence of 6.5/1000 PYFU [42]. Both of these studies had earlier follow-up to 2009 and 2007, respectively. The incidence of all cancers and NADCs presented here are also higher than in the general HIV-indeterminate population; for example, the incidence of all cancers in the general population in the United States from 2013 to 2017 was 4.9/1000 PYFU among males and 4.2/1000 PYFU among females [43], and in Europe in 2020, the age-adjusted incidence of all cancers was 5.4/1000 PYFU for all genders combined [44]. Whilst the higher incidence of all cancers in our analysis is likely driven in part by ADCs, especially in the earlier time periods, as mentioned previously, several studies have shown that people with HIV have an increased risk of NADCs compared to the general population [6–8].

A declining incidence of ADCs and infection-related cancers over time has been reported by many studies [8,9,11,17,18], and it is reassuring that this has now also been shown in this combined D:A:D and RESPOND population. After adjusting for time-

updated exposure to ARVs in a sensitivity analysis, rates of ADCs and infection-related cancers no longer significantly decreased, suggesting that the effect of ART use on CD4 count, at least in part, is the likely explanation for the reduction in the incidence of these cancers. Whilst the rate of decrease for ADC was faster in earlier years, there was no clear change in the rate of decrease in any notable time period, for example, before or after 2016, when treatment guidelines changed to recommend starting ART immediately, irrespective of the current CD4 count, or before or after recommendations for a particular ARV drug class [24,45]. We also found an interaction between baseline ART-experienced and the time period, showing that the incidence of all cancers decreased in individuals who were ART-naïve or ART-experienced with uncontrolled viremia, but not in those who were ART-experienced with a suppressed VL. This result was mainly driven by ADCs and is likely due to those who were ART-naïve or with uncontrolled viremia starting effective ART and becoming virally suppressed over time. This provides further evidence that ART use and the associated improvements in CD4 count is associated with the reduction in ADCs. It is likely that other preventative cancer strategies, such as human papillomavirus (HPV) vaccination or identifying pre-cancer lesions during screening for certain cancers, as per guideline recommendations, also contributed to the reduction in the incidence of these cancers over time; however, this information is not currently collected in D:A:D and RESPOND. Additionally, improvements in hepatitis B and C treatment in later years would likely have further impacted the results. All ADCs were included under infection-related cancers, and in future research assessing trends of individual cancers, it would be beneficial to determine whether the decreasing incidence is consistent across infection-related NADCs. Furthermore, we looked at the CD4 count at the time of cancer diagnosis, and whilst the CD4 count has increased at the time of diagnosis for NADCs over time, it has remained constant for ADCs, suggesting that early HIV diagnosis and provision of effective ART for individuals with low CD4 counts remains a priority.

Whilst ADCs and infection-related cancers decreased over time, we also showed that the incidence of NADCs, smoking-related cancers, and BMI-related cancers have increased slightly. Several studies have shown that the median BMI has increased over time amongst people with HIV [46,47], as in the general HIV-indeterminate population [48], and this may also increase the risk of BMI-related cancers [49]. A previous study in EuroSIDA found that the proportion of individuals who were overweight or obese increased over the study period with a median follow-up of 4 years; however, this did not translate into an increased risk of malignancies, although 4 years may be too short for cancer to develop [50]. Whilst BMI was strongly associated with an increased risk of BMI-related cancers in our analysis, we still found an increasing trend of BMI-related cancers, even after adjusting for BMI in our regression models. We did not assess BMI as the total time with elevated BMI, which could be a more important measure; however, we did include time-updated BMI, which we believe could capture some of the effect of this on BMI-related cancer rates. Toxicities associated with ART use also cannot be ruled out as a potential cause of these trends. As cancer can take many years to develop, there are few large studies able to assess whether use of contemporary ARVs are associated with an increased risk of NADCs [26,27,29], or whether cancer trends have changed throughout different ART-eras, when many different ARVs have been used. Some ARVs, such as dolutegravir and tenofovir alafenamide, have been shown to be associated with weight gain. Whilst some studies have only compared these ARVs to weight-suppressive alternatives, a recent RESPOND analysis used lamivudine, a weight-neutral ARV, as the comparator, and still found an association between dolutegravir and tenofovir alafenamide and weight gain [51–53]. It is possible that this weight gain could translate into an increase in the incidence of clinical outcomes, including BMI-associated cancers, and more research is needed to better understand the implications of this weight gain, as well as the trends in BMI-related cancers. Smoking-related cancers also increased slightly over time in our analysis. The prevalence of smoking amongst people with HIV is notably higher than in the general population, and the strong association between smoking and cancer is well described [22,54–56]. However, several

studies have also shown that the prevalence of smoking is declining over time [57,58]. Yet, the increasing trend shown here suggests that the effects of less smoking may not yet have translated into a reduction in smoking-related cancers in people with HIV. A previous analysis in D:A:D showed that the risk of lung cancer remained elevated more than 5 years after smoking cessation when compared to non-smokers [59]. Other important factors that may provide further insight into the residual effect of smoking on cancer risk, even after cessation, include the total pack-years of smoking or passive smoking; however, these are not currently collected in D:A:D and RESPOND. Additionally, some types of lung cancers, for example, adenocarcinomas, may not be related to smoking, and these cancers have been shown to be increasing both in people with HIV and in the general population [60]. We were unable to distinguish different lung cancer subtypes in our analysis, and therefore, all lung cancers were included as smoking-related. Despite this, we believe continued efforts to implement smoking cessation programs are needed.

Cancer trends were re-assessed after accounting for demographics, comorbidities, and HIV-related factors, with similar results found compared to when only taking into account the increasing age of the population through age standardisation. This suggests that changes in these factors over time are not fully explaining the cancer trends seen, and there are likely more factors that may be playing a part. Other factors potentially affecting cancer trends include lifestyle factors, such as alcohol use and the presence of other viruses shown to be associated with an increased risk of infection-related cancers, such as HPV or Epstein–Barr virus, all of which are not routinely collected in D:A:D and RESPOND [61–66]. The use of preventative measures for cancers, such as cancer screening and HPV vaccination, have changed over time; however, their impact may take more years to be observed, and we are unlikely to be able to see the impact, especially of HPV vaccination, over the time period studied here [59,67]. It is, therefore, important for further research to be conducted to identify causes of the trends presented, and for cancer trends to continue to be monitored in future years.

As our analysis included follow-up from 2006 to 2021, we were able to assess cancer trends across different ART-eras. Our results suggest that the trends seen were fairly consistent across the study period, and the introduction of more contemporary ARVs did not seem to impact our findings.

Limitations

Results from these analyses should be considered with limitations in mind. The populations included were comparatively young and, therefore, at a lower risk of cancer, which increases as individuals age. Whilst we were able to include a long follow-up in the analysis by combining data from 2 cohort collaborations, the median follow-up was 8.4 years, which may still be too short for some individuals, particularly younger participants, to develop cancer. We also excluded participants without follow-up data or those who did not satisfy the RESPOND inclusion criteria, and this may have introduced selection bias, although the baseline characteristics of individuals who were excluded were similar to those included. The two cohort collaborations include participants from Europe and Australia only, which may limit the generalisability of our results outside of these regions. As mentioned previously, there may also be factors explaining the cancer trends seen, such as family history of cancer or cancer screening, which we did not collect. For BMI-related cancers, individuals did not have to be at a specific BMI to qualify as having a BMI-related cancer. Additionally, when considering the effect of BMI on these cancer trends, we did not assess BMI as the total time with elevated BMI; however, we did include time-updated BMI, which we believe could capture some of the effect of this on BMI-related cancer rates. There are also some missing data in the cohorts, including for some key variables, such as smoking status and BMI, and therefore, the impact of these factors on cancer trends may have been underestimated. It was also not possible to fully assess the impact of specific ARVs on these cancer trends, although we were able to adjust for ART-experienced and cumulative exposure to drug classes, and there is limited

evidence in the literature of any specific ARVs being associated with an increased risk of cancer. Finally, we did not assess time trends for individual cancers, as this analysis was intended to provide an overview of the changes in cancer groups, and even longer follow-up is required for adequately detailed analyses of several less common cancers. It is likely that there is some heterogeneity amongst the groups of smoking-, BMI-, and infection-related cancers, and future analyses of D:A:D and RESPOND will focus on trends of individual cancers.

Despite these limitations, by combining data from 2 large international cohorts, we were able to assess temporal trends over 15 years from studies with similar designs and rigorous data collection and almost half a million PYFU.

5. Conclusions

In conclusion, we found that the age-standardised incidence of cancer overall has remained fairly constant over time from 2006 to 2021. ADCs and infection-related cancers have significantly decreased over time, whilst NADCs, smoking-related cancers, and BMI-related cancers have increased slightly. These results show the need for better prevention strategies to reduce the incidence of smoking- and BMI-related cancers, in particular. Our data also suggest that initiatives to reduce the incidence of several infection-related cancers and ADCs, such as earlier HIV diagnosis and provision of ART, have been somewhat effective. Further research into individual cancer trends is needed to better understand the causes of the cancer trends presented here.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/cancers15143640/s1>, Table S1: Cancers reported during follow-up, split into AIDS-defining and non-AIDS-defining cancers; Table S2: Cancers reported during follow-up, split by infection-related, smoking-related, and BMI-related cancers; Figure S1 Median CD4 count at time of cancer diagnosis for: (a) all cancer; (b) non-AIDS defining cancers; (c) AIDS defining cancers; Figure S2 Median CD4 count at time of cancer diagnosis for: (a) all cancer; (b) non-AIDS defining cancers; (c) AIDS defining cancers; Table S3: Results from a range of sensitivity analyses for all cancer, AIDS-defining cancer, non-AIDS-defining cancer; Table S4: Results from a range of sensitivity analyses for infection-related cancer, smoking-related cancer, and BMI-related cancer.

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Informed Consent Statement: Participants consented to share data with RESPOND according to local requirements. Participants were pseudonymised at enrolment by assignment of a unique identifier by the participating cohort before data transfer to the main RESPOND database. According to national or local requirements, all cohorts have approval to share data with RESPOND. Ethical approval was obtained, if required, from the relevant bodies for collection and sharing of data. Data are stored on secure servers at the RESPOND coordinating centre in Copenhagen, Denmark, in accordance with current legislation and under approval by The Danish Data Protection Agency (approval number 2012-58-0004, RH-2018-15, 26 January 2018), under the EU General Data Protection Regulation (2016/679). All participating cohorts followed local or national guidelines or regulations regarding patient consent and ethical review. Of the countries with participating cohorts, only Australia and Switzerland require specific ethical approval for the entire D:A:D cohort in addition to that required for their national cohorts (the Australian HIV Observational Database and the Swiss HIV Cohort Study); France (Nice and Aquitaine cohorts), Italy (ICONA cohort), and Belgium (Brussels Saint-Pierre cohort) do not require specific ethical approval more than that required for the individual cohorts; and the Netherlands (AIDS Therapy in the Netherlands project) does not require any specific ethical approval, because data are provided as part of HIV care. For the EuroSIDA study, which includes the data from the Barcelona Antiretroviral Surveillance Study and Swedish cohorts, among participants from many European countries, each participating site has a contractual obligation to ensure that data collection and sharing are conducted in accordance with national legislation; each site's principal investigator either maintains appropriate documentation from an ethical committee (if required by law) or has a documented written statement to say that this is not required.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available because they are not anonymised. The present RESPOND data structure and a list of all collected variables and their definitions can be found online. For any inquiries regarding data sharing, please contact the RESPOND secretariat and Dorthe Raben, Director of Research Coordination (dorthe.raben@regionh.dk).

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Appendix A

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