Malignancies among children and young people with HIV in Western and Eastern Europe and Thailand

The European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) study group*

Objectives: Investigate trends over time and predictors of malignancies among children and young people with HIV.

Design: Pooled data from 17 cohorts in 15 countries across Europe and Thailand.

Methods: Individuals diagnosed with HIV and presenting to paediatric care less than 18 years of age were included. Time at risk began at birth for children with documented vertically acquired HIV, and from first HIV-care visit for others. Children were followed until death, loss-to-follow-up, or last visit in paediatric or adult care (where data after transfer to adult care were available). Rates of reported malignancies were calculated overall and for AIDS-defining malignancies (ADM) and non-AIDS-defining malignancies (NADM) separately. Risk factors for any malignancy were explored using Poisson regression, and for mortality following a malignancy diagnosis using Cox regression.

Results: Among 9632 individuals included, 140 (1.5%) were ever diagnosed with a malignancy, of which 112 (80%) were ADM. Overall, the rate of any malignancy was 1.18 per 1000 person-years; the rate of ADM decreased over time whereas the rate of NADM increased. Male sex, being from a European cohort, vertically acquired HIV, current severe immunosuppression, current viral load greater than 400 copies/ml, older age, and, for those not on treatment, earlier calendar year, were risk factors for a malignancy diagnosis. Fifty-eight (41%) individuals with a malignancy died, a median 2.4 months (IQR 0.6–8.8) after malignancy diagnosis.

Conclusion: The rate of ADM has declined since widespread availability of combination ART, although of NADM, there was a small increase. Mortality following a malignancy was high, warranting further investigation.

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Keywords: adolescents, children, Europe, HIV, malignancies, Thailand

Introduction

Cancer is relatively rare in childhood in the general population, with the incidence rate to 19 years of age across Western and Eastern Europe estimated at 0.14 per 1000 person-years [1]. However, as a result of immunosuppression, systemic inflammation, persistent HIV viremia, and increased susceptibility to oncogenic viruses, such as Epstein–Barr Virus (EBV) and human herpesvirus 8 (HHV-8), people with HIV are at higher risk of some malignancies, including both those considered AIDS-defining (ADM), such as Kaposi sarcoma and non-Hodgkin lymphoma, and non-AIDS-defining (NADM), such as Hodgkin lymphoma [2,3].

In adults living with HIV, studies have reported declining incidence of ADM but increasing incidence of NADM in recent years [4–6]. However, children who acquire HIV vertically have lifelong exposure to the virus, and their long-term risk of malignancies is unclear, with the only studies that have followed them into young adulthood limited by small sample sizes [7]. Studies in children have

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shown those on antiretroviral therapy (ART) and initiating ART at younger ages are at lower risk [8–10]. In this study, we describe rates, risk factors for malignancy and mortality following a malignancy diagnosis in children and young people in the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC).

Methods

Seventeen observational cohorts in EPPICC from 15 countries across Europe and Thailand contributed individual-level demographic, clinical, laboratory and treatment-related data, which were pseudo-anonymized and pooled electronically using a modified HIV Cohorts Data Exchange Protocol (HICDEP, www.hicdep.org). All cohorts received approval from local/national ethics committees.

All children diagnosed with HIV, presenting to paediatric HIV care before 18 years of age, and with more than 1 day of follow-up were included. Time at risk began at birth for those with vertically acquired HIV, or on the date first seen in HIV care (defined as their first $CD4^+$ cell count, viral load, use of ART or AIDS-defining event) for those with other or unknown modes of acquisition as date of HIV infection was often unknown. Data after transfer to adult care were available for some individuals but if not they were censored at their last visit in paediatric care. Individuals were followed until death, loss to follow-up, drop out from cohort (for example, if they moved clinic), or their last visit prior to 1 October 2016.

None of the contributing cohorts are linked to cancer registries, and so data on malignancy events were collected from routine HIV healthcare records. Cervical intraepithelial neoplasia, a precancerous condition, was not included in the analysis. Malignancies were categorized as ADM or NADM based on the US Centers for Disease Control and Prevention (CDC) 2014 surveillance criteria [11]. The number and rate (per 1000 person-years) of malignancy events were summarized over calendar time, overall and separately for ADM and NADM. To allow for the possibility of multiple malignancy diagnoses, rates were calculated as the number of malignancy events divided by the total duration of follow-up. Rates were presented among all patients, as well as among patients on 'stable ART', defined as those on ART for at least 6 months, who currently had viral load 400 copies/ml or less and with no HIV-related immunosuppression (defined based on WHO criteria as $CD4^+$ >35% for those age <1 year; >30% for 1 to <3 years; >25% for 3-<5 years; >500 cells/μl for ≥5 years [12]). Rates of specific malignancies were presented where more than one event was reported. Characteristics at the time of malignancy diagnoses were compared among those with an ADM or NADM, using a chi-squared or Fisher's exact test (where numbers were <5) for categorical variables and Wilcoxon's rank-sum test for continuous variables.

Risk factors for any malignancy were explored using Poisson regression. Factors considered included sex, region of cohort (UK/Ireland, Thailand, Russia/Ukraine, rest of Europe), mode of HIV acquisition (vertical vs. other). In addition, the following time-updated characteristics were considered (with measurements carried forward up to 12 months): current ART status (not initiated ART vs. <6 months since ART initiation vs. ≥6 months since ART initiation), current calendar year (<1996 vs. 1996–2003 vs. 2004–2009 vs. ≥2010), current age (<5 vs. 5 to <10 vs. 10 to <15 vs. ≥15 years), current WHO immunological stage (severe vs. not severe, with severe immunosuppression defined based on WHO criteria as $CD4^+$ <25% for those age <1 year; <20% for age 1 to <3 years; <15% for 3 to <5 years; <200 cells/μl or <15% for ≥5 years [12]), current viral load (≤400 vs. >400 copies/ml), and current BMI-for-age z-score (>2 vs. −2 to 2 vs. <−2, based on WHO reference data [13]). Ethnicity and place of birth could not be included given that one of the areas of focus was comparing by region, and there were few children born abroad or from different ethnic groups in Thailand and Russia/Ukraine; the effects of these variables in the other cohorts were explored in a supplementary analysis. Two-way interactions between current ART status, calendar year and age were considered, using a cut-off of $P = 0.15$ for inclusion. Associations were explored using univariable models, and all factors were included in a multivariable model. Missing data on sex (missing for <1% of patients), mode of HIV acquisition (5% of patients) and current immunological stage (48% of patient-time), viral load (48% of patient-time) and BMI-for-age z-score (66% of patient-time) were imputed using multiple imputation with chained equations; 20 imputed datasets were created, and coefficients combined using Rubin's rules [14]. Risk factors for ADM and NADM were subsequently explored separately, using the same methods.

The probability of all-cause mortality by 3 years after malignancy diagnosis was estimated using Kaplan–Meier methods, overall and by calendar year. Cox regression was used to explore associations between mortality and the following (at malignancy diagnosis, and categorized as above if not specified): calendar year, malignancy type (ADM vs. NADM), recent presentation to HIV care (<6 months vs. ≥6 months), sex, region, mode of HIV acquisition, age, ART status, WHO immunological stage and BMI-for-age z-score.

Events occurring prior to the date first seen in HIV care ($n = 1$) or with unknown diagnosis date ($n = 3$) in those with other/unknown mode of infection were excluded

Table 1. Patient characteristics.

	UK/Ireland (*N* = 2069)	Thailand (*N* = 877)	Russia/Ukraine (*N* = 2280)	Rest of Europe (*N* = 4406)	Total (*N* = 9632)
	n (%) or median (IQR)				
Sex					
Female	1090 (53%)	473 (54%)	1241 (54%)	2245 (51%)	5049 (52%)
Male	978 (47%)	404 (46%)	1036 (45%)	2160 (49%)	4578 (48%)
Unknown	1 (<0.5%)	0	3 (<0.5%)	1 (<0.5%)	5 (<0.5%)
Mode of HIV acquisition					
Vertical	1922 (93%)	874 (100%)	2083 (91%)	3473 (79%)	8352 (87%)
Blood transfusion	40 (2%)	2 (<0.5%)	8 (<0.5%)	557 (13%)	607 (6%)
Sexual contact	0	1 (<0.5%)	37 (2%)	45 (1%)	83 (1%)
Other	1 (<0.5%)	0	16 (1%)	56 (1%)	73 (1%)
Unknown	106 (5%)	0	136 (6%)	275 (6%)	517 (5%)
Ethnicity					
White	179 (9%)	0	264 (99%)	1455 (33%)	3898 (40%)
Black African	1616 (78%)	0	0	453 (10%)	2069 (21%)
Other	227 (11%)	877 (100%)	2 (<0.5%)	162 (4%)	1268 (13%)
Unknown	47 (2%)	0	14 (1%)	2336 (53%)	2397 (25%)
Born abroad					
Yes	1164 (56%)	16 (2%)	6 (<0.5%)	964 (22%)	2150 (22%)
No	876 (42%)	782 (89%)	2262 (99%)	3377 (77%)	7297 (76%)
Unknown	29 (1%)	79 (9%)	12 (1%)	65 (1%)	185 (2%)
Region of country of birth if born abroad					
Europe	22 (2%)	0	0	49 (5%)	71 (3%)
sub-Saharan Africa	654 (56%)	0	0	306 (32%)	960 (45%)
Other	29 (2%)	12 (88%)	0	64 (7%)	107 (5%)
Unknown	459 (39%)	2 (13%)	6 (100%)	545 (57%)	1012 (47%)
Entry to HIV care[a]					
<1996	719 (35%)	319 (36%)	6 (<0.5%)	2192 (50%)	3233 (34%)
1996–2003	954 (46%)	466 (53%)	622 (27%)	1470 (33%)	3515 (36%)
2004–2009	311 (15%)	77 (8%)	1109 (45%)	521 (12%)	1927 (20%)
≥2010	85 (4%)	15 (2%)	633 (28%)	223 (5%)	957 (10%)
Ever initiated ART	1847 (89%)	877 (100%)	2085 (91%)	3970 (90%)	8779 (91%)
Age at ART initiation (years)	6.7 (2.4–11.2)	6.5 (2.3–9.6)	3.0 (1.0–6.5)	3.8 (0.9–8.9)	4.3 (1.2–9.1)
Duration of follow-up (years)	16.1 (11.2–17.9)	15.2 (11.0–18.3)	8.4 (4.7–11.9)	13.9 (7.1–18.3)	12.9 (7.1–17.5)
Current follow-up status					
Still in paediatric care	837 (40%)	225 (26%)	1656 (73%)	1581 (36%)	4299 (45%)
Transferred to adult care	920 (44%)	70 (8%)	100 (5%)	931 (21%)	2021 (21%)
Dropped out of cohort	117 (6%)	338 (39%)	65 (3%)	227 (5%)	747 (8%)
Lost-to-follow-up	80 (4%)	170 (19%)	406 (18%)	994 (23%)	1650 (17%)
Died	115 (6%)	74 (8%)	53 (2%)	673 (15%)	915 (10%)
Data available after transfer to adult care	149 (16%)	70 (100%)	62 (62%)	272 (29%)	553 (27%)
Age at transfer to adult care (years)	17.7 (16.8–18.5)	17.7 (16.8–18.3)	17.9 (17.8–17.9)	18.7 (17.7–20.1)	18.1 (17.2–19.1)
Duration of follow-up in adult care (years)	2.8 (1.2–4.3)	2.8 (1.2–4.5)	1.4 (0.5–2.6)	3.6 (1.7–6.3)	2.8 (1.2–5.0)

ART, antiretroviral therapy; IQR, interquartile range.

from all analyses. Further, children with vertically acquired HIV who had an event with unknown diagnosis date ($n = 4$) were included in the overall malignancy rate but excluded from analyses of the rate over calendar time and of risk factors.

Statistical analyses were conducted using Stata 16.1 (StataCorp, College Station, Texas, USA).

Results

Overall, 9632 patients had more than 1 day of follow-up in paediatric HIV care, and were therefore, included in this analysis (Table 1). Two thousand and sixty-nine (21%) patients were from UK/Ireland, 877 (9%) from Thailand, 2280 (24%) from Russia or Ukraine, and 4406 (46%) from the rest of Europe. The mode of HIV acquisition was documented as vertically acquired for 8352 (87%) patients, blood transfusion for 607 (6%), sexual contact for 83 (1%), other modes for 73 (1%), and was unknown for 517 (5%). Three thousand eight hundred and ninety-eight (40%) children were white, 2069 (21%) were black African, 1268 (13%) were of other ethnicity, and ethnicity was not reported for 2397 (25%). The median duration of follow-up was 12.9 [interquartile range (IQR) 7.1–17.5] years, with a total of 118 418 person-years of follow-up, of which 87 072 person-years was among those born within the country of their cohort and 28 946 person-years those born outside. Eight thousand, seven hundred and seventy-nine (91%) patients ever initiated ART. Calendar year of entry to HIV care ranged from 1980 to 2016. At last follow-up, 4299 (45%) patients were still in paediatric care, 1650 (17%) had been lost to follow-up, 747 (8%) had dropped out for other reasons, 915 (10%)

Table 2. Malignancy events.

Event	$N=140$ [n (%)]
AIDS-defining malignancies	112 (80%)
Non-Hodgkin lymphoma	83
Diffuse large B-cell (immunoblastic or centroblastic)	43
Burkitt (classical or atypical)	11
Primary brain	10
Unspecified	19
Kaposi sarcoma	25
Cervical cancer	1
Unspecified	3
Non-AIDS-defining malignancies	27 (19%)
Hodgkin lymphoma	15
Hepatocellular carcinoma[a]	2
Leiomyosarcoma	1
Other[b]	8
Unspecified	1
Unspecified	1 (1%)

[a]One patient had hepatitis B co-infection, and one had hepatitis C co-infection.
[b]Description of the eight other non-AIDS-defining malignancies: brain ganglioglioma; ganglioneuroblastoma; chest wall tumour (unspecified); disseminated adenocarcinoma; malignant fibrous histiocytoma; neuroendocrine tumour of the pancreas; cystic teratoma; acute T-lymphoblastic leukaemia.

had died in paediatric care, and the remaining 2021 (21%) had transferred to adult care, of whom 553 (27%) had data available after transfer with a median duration of adult care follow-up of 2.8 (1.2, 5.0) years.

One hundred and forty (1.5%) patients had a malignancy event (Table 2). No patient experienced more than one event. Of the 140 events, 112 (80%) were ADM, with the most common being non-Hodgkin lymphoma ($n=83$) and Kaposi sarcoma ($n=25$). A further 27 (19%) were NADM, including Hodgkin lymphoma ($n=15$) and hepatocellular carcinoma ($n=2$, one each in patients co-infected with hepatitis B and C).

Across all events, two (1%) patients were diagnosed with a malignancy prior to entry to HIV care, 8 (6%) were diagnosed at the same time as entry to HIV care, and 19 (14%) patients were diagnosed within 6 months. Among these 29 patients, 22 acquired HIV through vertical transmission [median age at malignancy diagnosis 5.1 (IQR 2.8–9.4) years], two through blood transfusion, three through sexual contact, and the mode of acquisition was unknown for three. Malignancy diagnoses among those born abroad were more likely to be before or soon after entering HIV care, compared with those born within the country of cohort [12/31 (39%) vs. 17/106 (16%), $P=0.007$]. Five events (four non-Hodgkin lymphoma and one hepatocellular carcinoma) occurred after transfer to adult care, at a median (IQR) age of 24.4 (18.8–24.9) years.

A higher proportion of those with an ADM were diagnosed within 6 months of entry to HIV care [23% ($n=26$) vs. 7% ($n=2$), $P=0.106$] and a lower proportion had previously been on ART [62% ($n=67$) vs. 96% ($n=26$), $P<0.001$], compared with those with an NADM. Age [9.9 (IQR 4.6–14.6) vs. 10.1 (8.0–16.4) years, $P=0.075$], $CD4^+$% [15 (6–23) vs. 19 (9–25), $P=0.273$] and the proportion with severe immunosuppression (58 vs. 36%, $P=0.133$) at malignancy diagnosis were similar between with ADM and NADM.

Of the 25 children diagnosed with Kaposi sarcoma, 44% were male, 40% were of black ethnicity, median age and CD4+% at malignancy diagnosis were 10.4 (5.4–14.3) years and 6 (2–19) respectively. There were 11 events of Burkitts lymphoma, of which 73% were in males and 45% in those of white ethnicity, occurring at a median 14.3 (4.7–17.7) years of age and $CD4^+$% of 16 (10–30).

Overall, the rate of any malignancy was 1.18 [95% confidence interval (CI) 1.00–1.40] per 1000 person-years, and was 0.35 (0.18–0.68) among stable patients. Of ADM specifically, the rate was 0.94 (0.79–1.14) and of NADM was 0.23 (0.16–0.33). The rates of non-Hodgkin lymphoma, Kaposi sarcoma and Hodgkin lymphoma were 0.70 (0.57–0.87), 0.21 (0.14–0.31) and 0.13 (0.08–0.21), respectively. The rate of any malignancy, ADM and NADM by calendar time are shown in Fig. 1. The rate of ADM was high and steady over time between 1990/1991 and 1996/1997 ($P=0.210$; ranging between 2.37 and 3.02), after which it dropped dramatically, ranging between 0.31 and 1.09 between 1996/1997 and 2014/2015, with a slight continued decrease over time ($P=0.064$). The rate of NADM increased over time from 0.21 in 1994/1995 to 0.53 in 2014/2015 ($P=0.060$).

Risk factors for any malignancy are shown in Table 3. In multivariable analysis, female individuals [adjusted rate ratio (aRR) 0.63 (95% CI 0.45–0.89) vs. male individuals, $P=0.009$] and those from the Thai cohort [aRR 0.16 (0.04–0.69) vs. UK/Ireland, $P=0.017$] were at lower risk of a malignancy. Individuals who did not acquire HIV vertically were at lower risk than those who did so vertically [other modes of infection aRR 0.58 (0.31–0.98) vs. vertical, $P=0.049$]. Those with current severe immunosuppression [severe immunosuppression aRR 3.95 (2.48–6.29) vs. no severe immunosuppression, $P<0.001$] and viral load more than 400 copies/ml [aRR 1.80 (1.01–3.71) vs. $\leq$400 copies/ml, $P=0.027$] were more likely to have a malignancy. There was evidence of an interaction between current ART status and each of current calendar year and current age (Fig. 2). There was no change in risk over calendar time among those who were not on ART ($P=0.414$) or who had been on ART less than 6 months ($P=0.999$), but among those on ART for more than 6 months, the risk decreased over time [1996–2003 aRR 0.41 (0.23–0.74), 2004–2009 aRR 0.25 (0.12–0.51), $\geq$2010 aRR 0.22 (0.10–0.51) vs. <1996, $P=0.001$]. There was a strong increase in risk with increasing current age among those not on

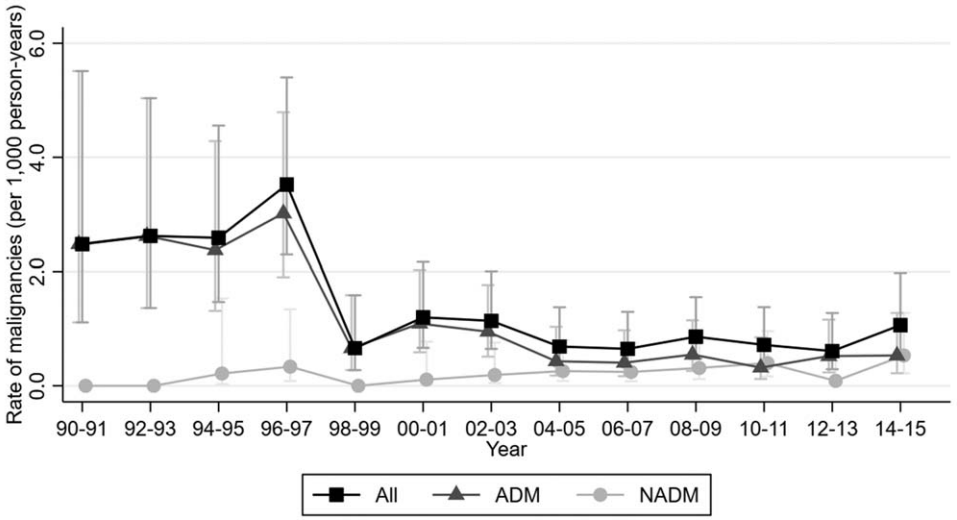

Fig. 1. Rates of malignancies over calendar time, overall and for AIDS-defining and non-AIDS-defining malignancies.

ART or on ART for less than 6 months, although less of an increase among those on ART at least 6 months. There was no evidence of an effect of current BMI-for-age z-score ($P = 0.114$). In a supplementary analysis for individuals from the UK/Ireland and rest of Europe regions, there was no evidence of an effect of ethnicity or place of birth in the adjusted model ($P = 0.588$, 0.955, respectively, data not shown).

Risk factors for ADM and NADM are shown in Supplementary Tables 1 and 2, http://links.lww.com/QAD/C163. Risk factors for ADM were similar to those for any malignancy. For NADM, only immunosuppression and mode of infection were found to be associated; those with current severe immunosuppression were at higher risk [aRR 2.91 (1.06–7.97) vs. not severe, $P = 0.038$] as were, in contrast to risk factors for any malignancy, those who did not acquire HIV vertically [aRR 3.13 (1.01–9.74) vs. vertical, $P = 0.049$].

Overall, 58 (41%) patients with a malignancy event were reported to have died. Three deaths occurred in children with an unknown date of malignancy event, and the remaining 55 died at a median 2.4 (IQR 0.6–8.8) months (range 0.0–18.8 years) after malignancy diagnosis. Of 10 deaths among patients with an NADM, 8 (80%) were reported to be because of their NADM, and two (20%) because of an AIDS-defining event. Of 44 deaths among patients with an ADM, 27 (61%) were because of an AIDS-defining event, nine (20%) were reported as HIV-related, two (5%) because of an invasive bacterial infection, and the cause was unknown for six (14%).

The probability of death by 3 years after diagnosis was 41.1% (95% CI 33.1–50.3%). Those diagnosed with a malignancy before 1996 were more likely to die by 3 years [68.0% (51.9–83.1%)], with no change over time from 1996 onwards [30.6% (19.7–45.6%), 25.2% (12.1–47.8%), 33.7% (17.5–58.6%) for 1996–2003, 2004–2009 and after 2010, respectively] (Supplementary Figure 1, http://links.lww.com/QAD/C163). In multivariable analysis, only earlier calendar year of malignancy diagnosis and vertically acquired HIV were associated with higher risk of mortality (Supplementary Table 3, http://links.lww.com/QAD/C163).

Discussion

In this analysis of nearly 10 000 patients seen in paediatric HIV care across Eastern and Western Europe and Thailand, we assessed rates and risk factors for malignancies and malignancy outcomes among children and young people with HIV. The rate of ADM declined markedly following the introduction and widespread availability of combination ART for children in 1996, with some evidence of an increase in NADM, although rates were similar to those of any malignancy in the general population [1]. Increased risk of a malignancy was associated with older age among those not on treatment, male sex, being from a European cohort, vertical HIV acquisition, severe immunosuppression and viral load greater than 400 copies/ml. High mortality was observed following a malignancy diagnosis with no improvement in recent years.

Across the whole time period, the rate of any malignancy was 1.18 per 1000 person-years, approximately eight times higher than the estimated 0.14 per 1000 person-years for children and young people in the general population in Europe [1]. The rate of ADM decreased markedly in the late 1990s following the introduction and widespread availability of paediatric combination ART, in

Table 3. Risk factors for any malignancy.

	Univariable			Multivariable		
	Rate ratio	95% CI	*P*	Rate ratio	95% CI	*P*
Demographics, at entry to HIV care						
Sex						
Female	0.59	0.42–0.83	0.002	0.63	0.45–0.89	0.009
Male	1.00	–		1.00	–	
Region						
UK/Ireland	1.00	–	<0.001	1.00	–	0.017
Thailand	0.15	0.04–0.64		0.16	0.04–0.69	
Russia/Ukraine	0.39	0.18–0.86		0.66	0.29–1.54	
Rest of Europe	1.58	1.05–2.36		1.28	0.81–2.02	
Mode of HIV acquisition						
Vertical	1.00	–	0.055	1.00	–	0.049
Other	1.68	1.00–2.86		0.58	0.31–0.98	
Time-updated						
WHO immune stage						
Not severe	1.00	–	<0.001	1.00	–	<0.001
Severe	4.56	3.11–6.69		3.95	2.48–6.29	
Viral load						
Suppressed	1.00	–	0.003	1.00	–	0.027
Not suppressed	2.42	1.37–4.27		1.80	1.01–3.71	
BMI-for-age *z*-score						
>2	1.00	–	0.023	1.00	–	0.114
−2 to 2	2.29	0.38–13.75		2.01	0.32–12.53	
<−2	7.58	0.78–73.41		5.25	0.49–56.12	
ART status						
Not on ART	1.00	–	0.001			
<6 months on ART	3.59	1.78–7.23				
≥6 months on ART	1.68	1.10–2.57				
Calendar year						
<1996	1.00	–	<0.001		Test for interaction: $P=0.144$	
1996–2003	0.60	0.39–0.94				
2004–2009	0.30	0.18–0.50				
≥2010	0.32	0.19–0.53				
Effect of time-updated calendar year among those not on ART			<1996	1.00	–	0.414
			1996–2003	1.41	0.52–3.84	
			2004–2009	0.63	0.17–2.42	
			≥2010	1.83	0.45–7.48	
Effect of time-updated calendar year among those on ART less than 6 months			<1996	1.00	–	0.999
			1996–2003	1.11	0.21–5.77	
			2004–2009	0.00	0.00 to >1000.00	
			≥2010	1.10	0.16–7.51	
Effect of time-updated calendar year among those on ART at least 6 months			<1996	1.00	–	0.001
			1996–2003	0.41	0.23, 0.74	
			2004–2009	0.25	0.12, 0.51	
			≥2010	0.22	0.10, 0.51	
Age (years)						
<5	1.00	–	0.033		Test for interaction: $P=0.088$	
5 to <10	1.29	0.80–2.07				
10 to <15	1.46	0.90–2.38				
≥15	2.02	1.26–3.25				
Effect of time-updated age among those not on ART			<5	1.00	–	0.003
			5 to <10	2.52	0.98–6.46	
			10 to <15	7.17	2.55–20.14	
			≥15	5.43	0.63–47.07	
Effect of time-updated age among those on ART less than 6 months			<5	1.00	–	0.036
			5 to <10	3.63	0.60–21.80	
			10 to <15	7.95	1.38–45.88	
			≥15	17.65	2.261–137.72	
Effect of time-updated age among those on ART at least 6 months			<5	1.00	–	0.019
			5 to <10	0.95	0.52–1.70	
			10 to <15	1.09	0.56–2.12	
			≥15	1.18	1.18–4.83	

CI, confidence interval; ART, antiretroviral therapy.

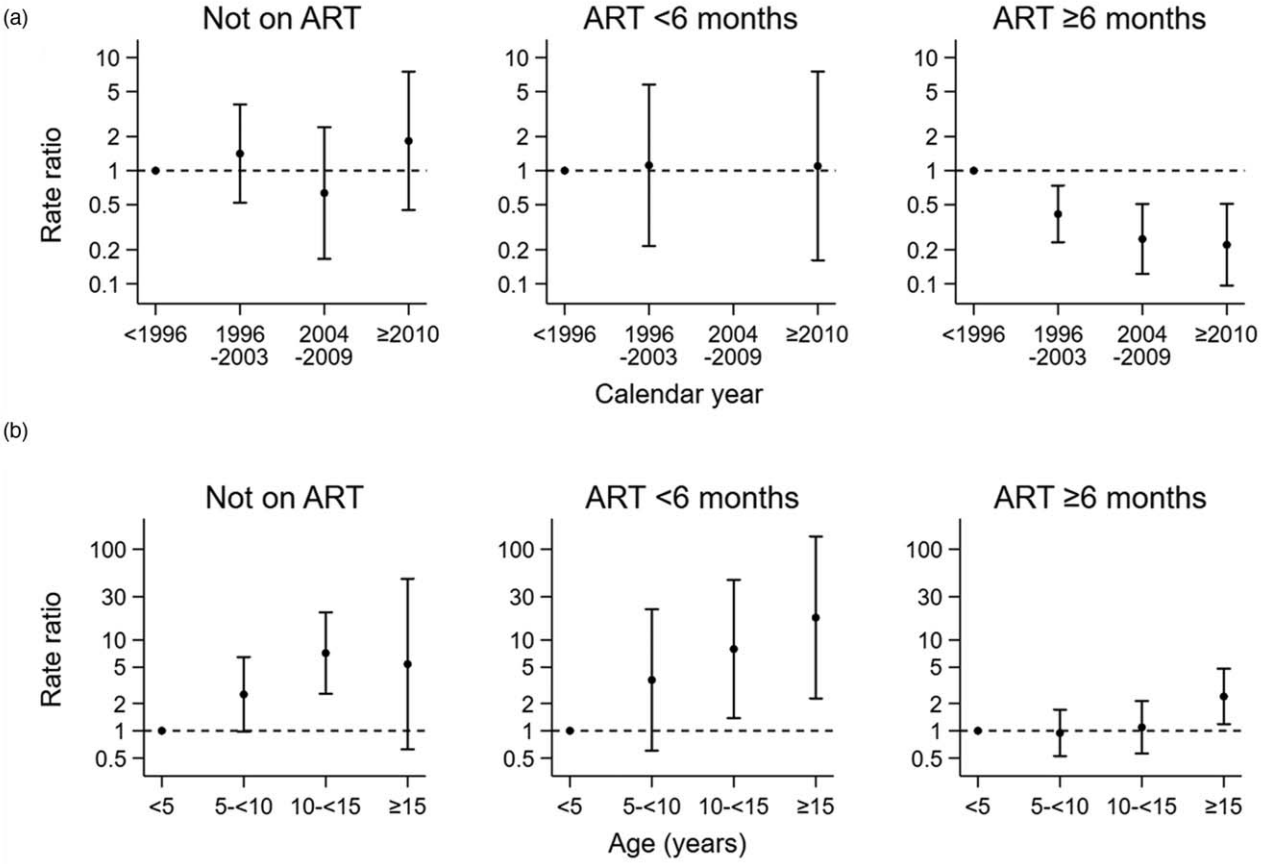

Fig. 2. Rate ratios for association between any malignancy and current calendar year (a) and current age (b) by antiretroviral therapy status. Adjusted for sex, region, mode of HIV acquisition, WHO immune stage, viral suppression and BMI-for-age *z*-score.

line with findings from adult studies [4–6]. Conversely, the rate of NADM increased over time as reported elsewhere [15], which may be because of increased survival among those with HIV, although some NADM, including Hodgkin lymphoma, are known to be related to HIV [16]. Reassuringly, among virologically suppressed, nonimmunosuppressed patients on ART in our study, the rate of any malignancy was very low, 0.35 per 1000 person-years, although double the general population rate. There may be reasons for this higher rate beyond HIV status; key differences between our population and that in the general population study [1] are our inclusion of young people beyond 19 years of age and our wider calendar time period. Further, there is some evidence that the rate of malignancies is higher in children from black ethnic groups in the general population, and so higher than average rates may be expected in our study, regardless of HIV infection [17]. The potential carcinogenic effect of ART is unclear [18].

In adjusted analysis, children from the Thai cohort were at lower risk of a malignancy compared with those from Europe. One explanation for this may be differing exposures to oncogenic viruses. There is some evidence of a lower seroprevalence of HHV-8, which is associated with Kaposi sarcoma, in Thailand compared with Europe and Africa [19,20]. A study estimating the risk of Kaposi sarcoma in children and adolescents reported no cases in Asia compared with rates between 11.4 and 85.8 per 100 000 person-years in sub-Saharan Africa and Europe [21]. The small number of Kaposi sarcoma events here precluded a similar analysis. Further, there is some evidence of lower rates of malignancies in the general paediatric population in Thailand compared with Europe (0.10 and 0.14 per 1000 person-years, respectively) [1,22].

The risk of a malignancy strongly increased with age among those not on or who had only recently started ART but there was less of an association, at least until adolescence, among those on treatment. Increasing risk among young people may be expected given the increased risk of malignancy in the general population in early adulthood [23]. Given that HIV infection is lifelong, the full elevated long-term risk may yet emerge, highlighting the importance of continued monitoring throughout adulthood of those with HIV acquired in childhood. Male individuals were at higher risk of ADM, which may be expected given an excess of non-Hodgkin lymphoma observed in the general male population [24].

Those with severe immune suppression and not virally suppressed were at higher risk, in line with other studies [9], reiterating the need for meeting UNAIDS targets for ART coverage, improving adherence, and reducing late diagnosis. Finally, those with vertically acquired HIV were shown to be at higher risk of ADM, yet lower risk of NADM, in adjusted analyses. Those with vertically acquired HIV are more likely to have been born abroad in our population, and so may have higher exposure to endemic oncogenic viruses, such as HHV-8 and EBV [25], although our analysis found no additional risk for those born abroad. Further, they had a longer duration of exposure to HIV. Reasons for the lower risk of NADM are unclear but may be related to their younger age, despite our adjustment for this.

Among those with a malignancy, all-cause mortality was high, with over 40% of children and young people reported to have died. In the general population, mortality by 3 years after a childhood cancer diagnosis in Europe has been estimated at 20% [26]. Although outcomes improved following the roll out of combination ART in 1996, worryingly, there was no improvement in mortality over time following this in our study, with approximately one-third of those diagnosed since 1996 dying within 3 years. This association was not explained by key characteristics, such as age at diagnosis, type of malignancy (ADM vs. NADM) or level of immunosuppression; vertically acquired HIV was the only other factor explored which was associated. In adults with HIV, malignancy outcomes have been shown to be broadly similar to the general population, although with poorer outcomes for some cancer types, including Hodgkin lymphoma [27,28]. Delayed malignancy diagnosis was believed to have contributed to poor outcomes in young adults diagnosed with a malignancy in the UK (some of whom are included here) [7]. Further, suboptimal treatment, perhaps because of concerns over the use of cancer treatment in children with immunosuppression [29], may have also contributed to the high mortality. No data on cancer treatment or stage at diagnosis, or any biological samples, were available to assess this here. Further, malignancy is associated with severe immunosuppression, which may have put patients at risk of dying from other causes. Among survivors, there may be an increased risk of secondary cancers, warranting regular screening [30].

Our study has several other limitations. Firstly, none of the cohorts were linked to cancer registries, so some cases may have been missed, with under-ascertainment and under diagnosis likely, especially in middle-income settings. However, estimated incidence rates were similar to other studies in children with HIV based on record linkage [8,31]. Secondly, limited data on co-infections with oncogenic viruses were available. Thirdly, despite the large size of our cohort, our ability to determine differences in risk factors for ADM and NADM was limited by the relatively small number of NADM events, and low power resulted in wide confidence intervals when estimating rates over time. The major strength of this study is the long duration of follow-up and long calendar period covered as well as the inclusion of data following transfer to adult care.

In conclusion, in this analysis of nearly 10 000 children and young people with HIV across Europe and Thailand, we report a decline in the rates of ADM since the introduction of combination ART, with the rate of any malignancies among those on ART, virally suppressed and immunologically well similar to that in the general population. There was an increased risk with age, in particular, in those not currently on ART, which requires continued monitoring as young people with vertically acquired HIV progress into adulthood. Linkage of paediatric and adult registries, as well as HIV, malignancy and death registries, is crucial. Even in recent years, one-third of individuals with a malignancy died within 3 years of diagnosis, which is very concerning; possible causes should be explored and steps taken to address this.

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Conflicts of interest

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