Clinical Infectious Diseases

MAJOR ARTICLE

HIV/AIDS

Kaposi Sarcoma Risk in HIV-Infected Children and Adolescents on Combination Antiretroviral Therapy From Sub-Saharan Africa, Europe, and Asia

The Pediatric AIDS-Defining Cancer Project Working Group for IeDEA Southern Africa, TApHOD, and COHERE in EuroCoord[a]

Background. The burden of Kaposi sarcoma (KS) in human immunodeficiency virus (HIV)–infected children and adolescents on combination antiretroviral therapy (cART) has not been compared globally.

Methods. We analyzed cohort data from the International Epidemiologic Databases to Evaluate AIDS and the Collaboration of Observational HIV Epidemiological Research in Europe. We included HIV-infected children aged <16 years at cART initiation from 1996 onward. We used Cox models to calculate hazard ratios (HRs), adjusted for region and origin, sex, cART start year, age, and HIV/AIDS stage at cART initiation.

Results. We included 24 991 children from eastern Africa, southern Africa, Europe and Asia; 26 developed KS after starting cART. Incidence rates per 100 000 person-years (PYs) were 86 in eastern Africa (95% confidence interval [CI], 55–133), 11 in southern Africa (95% CI, 4–35), and 81 (95% CI, 26–252) in children of sub-Saharan African (SSA) origin in Europe. The KS incidence rates were 0/100 000 PYs in children of non-SSA origin in Europe (95% CI, 0–50) and in Asia (95% CI, 0–27). KS risk was lower in girls than in boys (adjusted HR [aHR], 0.3; 95% CI, .1–.9) and increased with age (10–15 vs 0–4 years; aHR, 3.4; 95% CI, 1.2–10.1) and advanced HIV/AIDS stage (CDC stage C vs A/B; aHR, 2.4; 95% CI, .8–7.3) at cART initiation.

Conclusions. HIV-infected children from SSA but not those from other regions, have a high risk of developing KS after cART initiation. Early cART initiation in these children might reduce KS risk.

Keywords. Kaposi sarcoma; HIV; children; antiretroviral therapy; cohort study.

Human immunodeficiency virus (HIV)–infected children and adolescents are at increased risk of developing Kaposi sarcoma (KS) [1]. In the era of combination antiretroviral therapy (cART), reported KS incidence rates in HIV-infected children vary from 17 to 150/100 000 person-years (PYs) [2–6]. Although these KS incidence rates are generally lower than in the pre-cART era [1–3, 7], they still exceed the incidence rates of all cancer types combined in children from the general population. For example, the overall cancer incidence rate per 100 000 PYs is 14 in children and adolescents in Europe, 10 in eastern Africa, and 5 in southern Africa [8]. In addition, mortality from KS in HIV-infected children remains substantial in resource-limited regions [9, 10]. Median survival was less than 6 months in a recent trial from Malawi [10].

Immune deterioration following uncontrolled HIV replication increases the risk of developing KS in children coinfected with human herpesvirus 8 (HHV-8). HHV-8 seroprevalence in the general population differs across sub-Saharan Africa (SSA), Europe, and Asia. However, few studies reported HHV-8 seroprevalence data for HIV-infected children. Around 40% of HIV-infected infants in Zambia and 30% of children in South Africa (mean age, 5.5 years) are seropositive for HHV-8 [11, 12]. Children born in western Europe have a lower risk of HHV-8 coinfection than children born in SSA and other parts of the world [13]. HHV-8 seroprevalence among HIV-infected children from Asia has not been reported, but studies in HIV-infected adults indicate that HHV-8 seroprevalence is lower in this region than in SSA [14, 15].

cART suppresses HIV replication, restores immune function, and subsequently reduces the risk of developing KS [3, 5]. However, access to cART differs across regions. In 2013, pediatric cART coverage reached 95% in Europe but only about 25% in Africa and Southeast Asia [16]. The majority of HIV-infected children from low- and middle-income countries initiate cART when severely immunosuppressed [17]. African-born children who have migrated to Europe also start cART at older ages and in more immunosuppressed stages than children born in Europe [18, 19].

Despite these regional differences in HHV-8 exposure and access to healthcare, KS risk among HIV-infected children and adolescents has not been directly compared across regions. We collaborated with the International Epidemiologic Databases to Evaluate AIDS (IeDEA) and the Collaboration of Observational

Received 16 March 2016; accepted 21 July 2016; published online 30 August 2016.

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Clinical Infectious Diseases® 2016;63(9):1245–53

DOI: 10.1093/cid/ciw519

HIV Epidemiological Research in Europe (COHERE) in EuroCoord to compare KS incidence rates and associated risk factors in HIV-infected children and adolescents who initiated cART in eastern Africa, southern Africa, Europe, and Asia.

METHODS

Databases

We analyzed data from observational HIV cohorts that systematically collect data on KS in children and adolescents and participate in the IeDEA Southern Africa (IeDEA-SA) [20], the IeDEA Asia-Pacific's TREAT Asia Pediatric HIV Observational Database (TApHOD) [21], or the COHERE in EuroCoord [22]. IeDEA-SA includes 7 cART programs in South Africa, Zambia, and Zimbabwe that collect KS data in children and adolescents systematically [20] or obtain these data through a record linkage with pediatric oncology departments [5]. TApHOD combines data from 18 pediatric clinics in Cambodia, India, Indonesia, Malaysia, Thailand, and Vietnam. Data on HIV-infected children and adolescents from 11 cohorts in 9 European countries (Austria, Denmark, France, Germany, Greece, the Netherlands, Spain, the United Kingdom, and Ireland) were included through the COHERE in EuroCoord 2014 dataset. All included cohorts collect demographic, clinical, treatment, and outcome data on children and adolescents with HIV. Ethical approval for each cohort was obtained from local ethics committees or institutional review boards.

Inclusion Criteria and Definitions

We included all HIV-infected children and adolescents aged <16 years at cART initiation in or after 1996. We excluded children who initiated cART before enrollment into a cohort and children without follow-up on cART, including those who developed KS before initiating cART. Cohorts with ≤10 eligible children were excluded. KS cases were either histologically confirmed or clinically diagnosed only. Because risk of HHV-8 infection varies by place of residence and place of birth, we stratified the data by geographic region of the cohort (Asia, eastern Africa, southern Africa); among those in Europe, we stratified the data by the child's place of birth (European children of SSA origin and European children of non-SSA origin). Geographic regions were defined according to the United Nations classification and do not necessarily correspond to consortia regions [23]. We used World Health Organization (WHO) 2007 growth reference standards to calculate sex-standardized weight-for-age *z* scores (WAZ) at cART initiation for children aged <10 years at the time of measurement [24, 25]. A WAZ of below −3 was considered as severely underweight. Children aged ≥10 years were excluded from WAZ analyses because WAZ are not recommended as a growth measure in older children and adolescents [25]. CD4 cell count at cART initiation was defined as the measurement closest to initiation within 180 days before to 7 days after cART initiation. Children aged <5 years were excluded from CD4 cell count analyses because CD4% is recommended for this age group [26]. Immunodeficiency at cART initiation was categorized into no, mild, advanced, and severe according to WHO 2007 surveillance criteria [26]. Clinical HIV/AIDS stage at cART initiation was defined according to the US Centers for Disease Control and Prevention (CDC) criteria [27]. We defined cART as a regimen of at least 3 antiretroviral (ARV) drugs from any class, including protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors, and nonnucleoside reverse transcriptase inhibitors (NNRTIs). We considered KS diagnosed before or at cART initiation to be prevalent KS and KS diagnosed after cART initiation to be incident KS.

Statistical Methods

We calculated KS incidence rates by dividing the number of children who developed KS by PYs at risk. Time at risk was measured from cART initiation to KS diagnosis, last follow-up visit, death, or database closure, whichever occurred first. Observation time was not right censored at a specific age. We calculated KS incidence rates for the overall observation period and by time periods after cART initiation, that is, 0–3 months, 4–6 months, 7–12 months, 13–36 months, and >36 months. We ignored interruptions and treatment changes to cART. Crude and adjusted Cox proportional hazards models were used to describe risk factors for incident KS. We assessed the following risk factors: cohort region and child's origin (eastern Africa, southern Africa, Europe with SSA origin, Europe with non-SSA origin, Asia), sex, age at cART initiation, first-line cART regimen (NNRTI-based, PI-based, other regimen), calendar period of cART initiation (1996–2003, 2004–2007, 2008–2014), CD4 cell count at cART initiation (<200 cells/μL, ≥200 cells/μL), CD4% at cART initiation (<10%, 10%–19%, ≥20%), and CDC stage at cART initiation (A/B, C). The multivariable Cox model included region and origin, sex, age, CDC stage, and calendar period of cART initiation. In sensitivity analyses, we censored follow-up time at 1 year after cART initiation, and we restricted the analyses to children at increased risk of HHV-8 infection, that is, those in eastern and southern Africa and children of SSA origin in Europe [11–13]. Results are presented as medians with interquartile ranges (IQRs), percentages, incidence rates per 100 000 PYs with 95% confidence intervals (CIs), or hazard ratios (HRs) with 95% CIs. All analyses were done in Stata 13.1 (Stata Corporation, College Station, Texas).

RESULTS

Study Population

The database included 35 133 HIV-infected children and adolescents. We excluded 3324 because they did not initiate cART or had a missing cART start date. Another 6818 children were excluded for reasons detailed in Figure 1. We excluded 53 children with prevalent KS—26 from eastern Africa, 22 from southern Africa, 3 of SSA origin in Europe, and 2 from Asia. Children with prevalent KS were more often female than those with

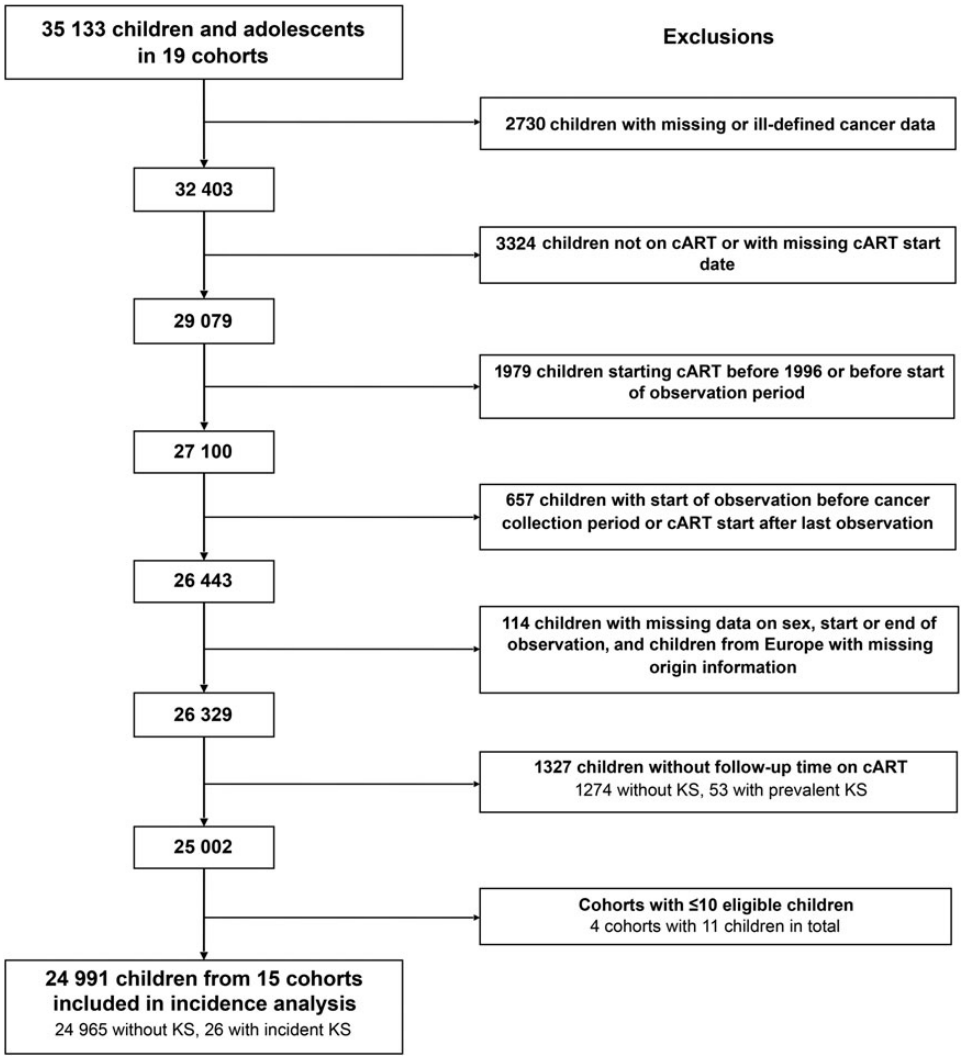

Figure 1. Identification of study population for analysis. The flow diagram shows the number of included and excluded children and adolescents. Abbreviations: cART, combination antiretroviral therapy; KS, Kaposi sarcoma.

incident KS (43% vs 31%), but median age at KS diagnosis was similar (both 9.6 years). We included data on 24 991 children and adolescents from 16 countries in eastern Africa (Zimbabwe and Zambia), southern Africa (South Africa), Europe (Denmark, France, Germany, Ireland, the Netherlands, Spain, and the United Kingdom), and Asia (Cambodia, India, Indonesia, Malaysia, Thailand, and Vietnam). Most children included in eastern Africa were located in Zambia (91%, n = 10 173); in Europe, the majority came from the United Kingdom and Ireland (63%, n = 1005), and in Asia, 43% (n = 1325) were located in Thailand. In Europe, 41% (n = 658) of the included children originated from SSA; 67% (n = 444) of these were born in eastern Africa. Excluded children were less likely to live in eastern Africa than included children (27% vs 45%), but the sex distribution was the same (both 50%).

Median age at cART initiation was 5.0 years (IQR, 1.8–9.1) and varied across regions (Table 1). It was lowest in southern Africa and in European children of non-SSA origin and highest in European children of SSA origin. More than one third of children in southern Africa and Europe were treated with PI-based first-line regimens, but ARVs from this class were prescribed rarely in Asia (5%) and eastern Africa (<1%). In Europe, most children of non-SSA origin (52%) initiated cART between 1996 and 2003, whereas only 34% of children of SSA origin living in Europe and even fewer children from Asia and eastern and southern Africa initiated cART before 2004. About 20% of children aged <10 years in eastern Africa, southern Africa, and Asia were severely underweight at cART initiation, whereas <5% of children aged <10 years were severely underweight in Europe. Children in Asia tended to start cART with lower CD4 cell counts and lower CD4% than those from other regions. Overall, the majority of children (63%) started cART with advanced or severe immunodeficiency; however, for 21% (n = 5314), we could not determine the degree of immunosuppression at cART initiation.

Table 1. Characteristics of Included Children and Adolescents

Characteristic	Eastern Africa N (%)	Southern Africa N (%)	Europe, SSA Origin N (%)	Europe, Non-SSA Origin N (%)	Asia N (%)
All children	11 163 (100)	9174 (100)	658 (100)	934 (100)	3062 (100)
Median follow-up time (IQR) (y)	1.6 (0.5–3.4)	2.4 (0.9–4.6)	5.2 (2.6–8.4)	8.0 (4.1–11.7)	4.4 (2.1–6.5)
Sex					
Boys	5547 (50)	4582 (50)	335 (51)	454 (49)	1569 (51)
Girls	5616 (50)	4592 (50)	323 (49)	480 (51)	1493 (49)
Median age at cART initiation (IQR) (y)	6.1 (2.3–10.3)	3.4 (1.0–7.3)	8.7 (5.0–12.1)	3.3 (0.6–8.8)	5.8 (3.0–8.8)
Age at cART initiation (y)					
0–4	4834 (43)	5551 (61)	163 (25)	545 (58)	1316 (43)
5–9	3344 (30)	2539 (28)	219 (33)	199 (21)	1205 (39)
10–15	2985 (27)	1084 (12)	276 (42)	190 (20)	541 (18)
Median WAZ at cART initiation (IQR)[a]	−2.0 (−3.0 to −1.0)	−1.7 (−2.7 to −0.7)	−0.4 (−1.2 to 0.4)	−0.4 (−1.5 to 0.5)	−2.2 (−3.2 to −1.2)
WAZ at cART initiation[a]					
<−3	1858 (23)	1343 (17)	7 (2)	27 (4)	564 (22)
−3 to <−2	1733 (21)	1408 (17)	22 (6)	36 (5)	513 (20)
−2 to <−1	1929 (24)	1795 (22)	50 (13)	88 (12)	490 (19)
≥−1	1774 (22)	2088 (26)	193 (51)	265 (36)	419 (17)
Missing	884 (11)	1456 (18)	110 (29)	328 (44)	535 (21)
First-line cART regimen					
Nonnucleoside reverse-transcriptase inhibitors based	11 056 (99)	4980 (54)	432 (66)	434 (46)	2859 (93)
Protease inhibitor based	13 (<1)	4174 (46)	205 (31)	449 (48)	157 (5)
Other cART	94 (1)	20 (<1)	21 (3)	51 (5)	46 (2)
Year of cART initiation					
1996–2003	3 (<1)	236 (3)	221 (34)	484 (52)	461 (15)
2004–2007	4958 (44)	4496 (49)	215 (33)	258 (28)	1433 (47)
2008–2014	6202 (56)	4442 (48)	222 (34)	192 (21)	1168 (38)
Centers for Disease Control and Prevention stage at cART initiation					
A/B	9127 (82)	8029 (88)	528 (80)	701 (75)	2234 (73)
C	925 (8)	907 (10)	65 (10)	157 (17)	370 (12)
Missing	1111 (10)	238 (3)	65 (10)	76 (8)	458 (15)
Immunodeficiency at cART initiation[b]					
None/mild	1754 (16)	1470 (16)	156 (24)	279 (30)	331 (11)
Advanced/severe	6871 (62)	5672 (62)	446 (68)	473 (51)	2225 (73)
Missing	2538 (23)	2032 (22)	56 (9)	182 (19)	506 (17)
Median CD4 cell count at cART initiation (IQR) (cells/μL)[c]	241 (120–403)	265 (108–466)	259 (135–406)	290 (140–469)	118 (26–300)
CD4 cell count at cART initiation (cells/μL)[c]					
<200	2272 (36)	1103 (30)	172 (35)	105 (27)	940 (54)
≥200	3175 (50)	1734 (48)	290 (59)	214 (55)	567 (32)
Missing	882 (14)	786 (22)	33 (7)	70 (18)	239 (14)
Median CD4% at cART initiation (IQR)	14 (9–19)	14 (8–21)	14 (8–20)	17 (11–28)	9 (3–16)
CD4% at cART initiation					
<10%	2139 (19)	2194 (24)	168 (26)	150 (16)	1353 (44)
10–19%	3206 (29)	2882 (31)	260 (40)	240 (26)	807 (26)
≥20%	1617 (14)	1914 (21)	148 (22)	316 (34)	373 (12)
Missing	4201 (38)	2184 (24)	82 (12)	228 (24)	529 (17)

Abbreviations: cART, combination antiretroviral therapy; IQR, interquartile range; SSA, sub-Saharan African; WAZ, weight-for-age *z* scores.

[a] Weight-for-age *z* scores only calculated for children <10 years at time of measurement.

[b] World Health Organization 2007 surveillance definition of immunodeficiency [26].

[c] Children aged <5 years were excluded from the analysis of CD4 cell counts.

Children with missing CD4 data were younger than those for whom data were available (median age, 3.5 years vs 5.5 years), but the proportion with advanced CDC stage C was similar (9% vs 10%). The median follow-up time after cART initiation was 2.3 years (IQR, 0.8–4.5 years) and varied across regions; it was longest in European children of non-SSA origin (8.0 years) and shortest in children from eastern Africa (1.6 years). At the end of follow-up, median age ranged between 7.0 years in

Table 2. Kaposi Sarcoma (KS) Incidence Rates per 100 000 Person-Years and Hazard Ratios for Developing KS in Children and Adolescents who Initiated Combination Antiretroviral Therapy

Characteristic	Patients (N)	Person-Years	Cases (N)	Incidence Rate (95% CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Overall	24 991	74 456	26	34.9 (23.8–51.3)	. . .	. . .
Region and origin						
Eastern Africa	11 163	23 313	20	85.8 (55.3–133.0)	1.0	1.0
Southern Africa	9174	26 337	3	11.4 (3.7–35.3)	0.2 (.0–.5)	0.1 (.0–0.6)
Europe, SSA origin	658	3694	3	81.2 (26.2–251.8)	1.8 (.5–6.1)	1.0 (.2–6.4)
Europe, non-SSA origin	934	7428	0	0 (0–49.8)	. . .	. . .
Asia	3062	13 684	0	0 (0–27.0)	. . .	. . .
Sex						
Boys	12 487	37 448	18	48.1 (30.3–76.3)	1.0	1.0
Girls	12 504	37 009	8	21.6 (10.8–43.2)	0.4 (.2–1.0)	0.3 (.1–.9)
Age at cART initiation (y)						
0–4	12 409	34 923	7	20.0 (9.6–42.0)	1.0	1.0
5–9	7506	25 431	7	27.5 (13.1–57.7)	1.5 (.5–4.2)	1.2 (.4–4.3)
10–15	5076	14 102	12	85.1 (48.3–149.8)	3.9 (1.5–10.0)	3.4 (1.2–10.1)
Weight-for-age *z* score at cART initiation[b]						
<−3	3799	9709	0	0 (0–38.1)	. . .	. . .
−3 to <−2	3712	10 408	2	19.2 (4.8–76.8)	1.4 (.2–9.6)	. . .
−2 to <−1	4352	12 870	7	54.4 (25.9–114.1)	3.9 (.8–19.0)	. . .
≥−1	4739	15 817	2	12.6 (3.2–50.6)	1.0	. . .
Missing	3313	11 550	3	. . .	. . .	. . .
First-line cART regimen						
Nonnucleoside reverse-transcriptase inhibitors based	19 761	57 502	25	43.5 (29.4–64.3)	1.0	. . .
Protease inhibitor based	4998	15 945	1	6.3 (.9–44.5)	0.2 (.0–1.2)	. . .
Other cART	232	1009	0	. . .	. . .	. . .
Year of cART initiation						
1996–2003	1405	12 252	2	16.3 (4.1–65.3)	1.0	1.0
2004–2007	11 360	44 121	18	40.8 (25.7–64.8)	1.3 (.3–5.5)	0.4 (.0–3.6)
2008–2014	12 226	18 084	6	33.2 (14.9–73.9)	0.5 (.1–2.8)	0.2 (.0–2.1)
Centers for Disease Control and Prevention stage at cART initiation						
A/B	20 619	60 261	17	28.2 (17.5–45.4)	1.0	1.0
C	2424	7027	4	56.9 (21.4–151.7)	2.2 (.7–6.6)	2.4 (.8–7.3)
Missing	1948	7168	5	. . .	. . .	. . .
CD4 cell count at cART initiation (cells/μL)[c]						
<200	4592	15 331	8	52.2 (26.1–104.3)	1.0	. . .
≥200	5980	18 265	5	27.4 (11.4–65.8)	0.5 (.2–1.5)	. . .
Missing	2010	5937	6	. . .	. . .	. . .
CD4% at cART initiation						
<10%	6004	20 563	7	34.0 (16.2–71.4)	1.0	. . .
10–19%	7395	22 032	3	13.6 (4.4–42.2)	0.4 (.1–1.4)	. . .
≥20%	4368	12 003	2	16.7 (4.2–66.6)	0.4 (.1–2.1)	. . .
Missing	7224	19 858	14	. . .	. . .	. . .

Abbreviations: cART, combination antiretroviral therapy; CI, confidence interval; HR, hazard ratio; SSA, sub-Saharan African.

[a] Adjusted for region and origin, sex, age, year of ART initiation, and Centers for Disease Control and Prevention stage at cART initiation. Number of children and adolescents included in multivariable model, N = 23 043.

[b] Weight-for-age *z* scores only calculated for children aged <10 years at time of measurement.

[c] Children aged <5 years were excluded from the analysis of CD4 cell counts.

children from southern Africa and 15.1 years in children of SSA origin in Europe.

KS Incidence Rates and Risk Factors

Among 24 991 children and adolescents, 26 developed incident KS during 74 456 PYs at risk, for an overall KS incidence rate of 35/100 000 PYs (95% CI, 24–51; see Table 2). Of the 26 incident KS cases, 20 were observed in eastern Africa, 3 in southern Africa, and 3 in Europe. Median age at KS diagnosis was 9.6 years (IQR, 6.4–15.2). All KS cases in Europe occurred in children of SSA origin. The KS incidence rate was higher in eastern Africa (86/100 000 PYs; 95% CI, 55–133) than in southern Africa (11/100 000 PYs; 95% CI, 4–35). In Europe, the KS incidence rate

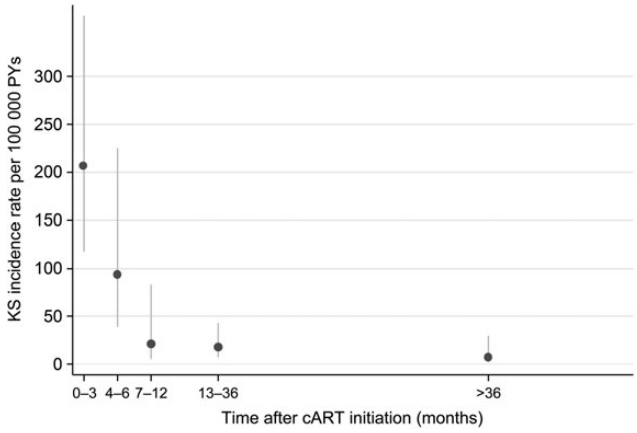

Figure 2. Kaposi sarcoma incidence rates with 95% confidence intervals in human immunodeficiency virus–infected children and adolescents by time after combination antiretroviral therapy initiation. Abbreviations: cART, combination antiretroviral therapy; KS, Kaposi sarcoma; PYs, person-years.

was 81/100 000 PYs (95% CI, 26–252) in children of SSA origin but 0/100 000 PYs (95% CI, 0–50) in those of non-SSA origin. During 13 684 PYs in children from Asia, no incident KS case was recorded (KS incidence rate 0/100 000 PYs; 95% CI, 0–27). The overall KS incidence rate was highest in the first 3 months after cART initiation (207/100 000 PYs; 95% CI, 117–364) and declined steeply thereafter (Figure 2). Of the 26 incident KS cases, 12 (46%) were diagnosed within the first 3 months after cART initiation. These early KS cases had initiated cART with lower median CD4 cell counts than children diagnosed with KS more than 3 months after cART initiation (90 cells/μL vs 310 cells/μL). None of the children who developed KS were diagnosed with non-Hodgkin lymphoma before or after KS diagnosis.

In univariable analysis, KS risk was higher in European children of SSA origin compared with those in eastern Africa (crude HR, 1.8; 95% CI, .5–6.1; see Table 2). However, the risk became similar (adjusted HR [aHR], 1.0; 95% CI, .2–6.4) after adjusting for sex, calendar period of cART initiation, age, and CDC stage at cART initiation. KS risk was lower in southern Africa compared with eastern Africa (aHR, 0.1; 95% CI, .0–.6) and increased with age at cART initiation (10–15 years vs 0–4 years; aHR, 3.4; 95% CI, 1.2–10.1) and advanced CDC stage at cART initiation (C vs A/B; aHR 2.4; 95% CI, .8–7.3). KS risk was lower in girls than in boys (aHR, 0.3; 95% CI, .1–.9). In multivariable analysis, especially after adjustment for region and origin, KS risk seemed to decrease in more recent calendar periods, but CIs overlapped widely. When we restricted the analysis to children at increased risk of HHV-8 coinfection, that is, those in eastern and southern Africa and children of SSA origin in Europe, HRs for developing KS remained similar to those estimated in the main analysis (data not shown). When we censored follow-up time at 1 year after cART initiation, KS incidence rates per 100 000 PYs were 162 in children from eastern Africa, 39 in children from southern Africa, 320 in children of SSA origin in Europe, and 0 in children of non-SSA origin in Europe and in Asia (Supplementary Table 1). However, crude and adjusted HRs for developing KS did not change much compared with the main analysis (Supplementary Table 1).

DISCUSSION

HIV-infected children and adolescents from eastern and southern Africa and those of SSA origin living in Europe were at highest risk of developing KS after cART initiation. The risk of developing KS decreased with time after cART initiation. KS risk was lower in girls than in boys and increased with age and advanced HIV/AIDS stage at cART initiation. We did not detect any incident KS cases in children from Asia and in European children of non-SSA origin.

We are the first to directly compare KS incidence rates across regions and to specifically examine risk factors for developing KS in HIV-infected children on cART. Previous research examined overall cancers in HIV-infected children and did not have sufficient cases for a KS-specific analysis [2, 3]. However, some of the children from eastern and southern Africa were included in previous studies [5, 6].

Several limitations of our study need to be addressed. Many HIV treatment programs in eastern and southern Africa only start following children after cART initiation. Therefore, we restricted this comparative analysis to children who initiated cART. The children in this analysis might not be representative of all HIV-infected children in the included geographic regions. For example, all southern African cART programs were located in urban areas of South Africa, and the majority of children from eastern Africa lived in Zambia. KS diagnoses in eastern Africa were often based on clinical assessment without histological confirmation, which might have led to an over- or underestimation of KS incidence rates in children from this region. For southern Africa, KS ascertainment was improved through a record linkage with pediatric oncology departments [5]. HIV RNA data and CD4 measurements were missing for 65% and 21% of included children, respectively. This limited our ability to explore the impact of these biological markers on KS risk. Similarly, CDC stage data were missing for 8% of included children and 19% of KS cases, which reduced the precision of the CDC stage effect estimate. However, the effect size was still considerable. Data on HHV-8 infection status were not available.

In our analyses, all KS cases in Europe were diagnosed in children born in SSA. This has not been described before; however, in Europe, KS risk is higher in HIV-infected adults from SSA than in others [28, 29]. Our finding of zero incident KS cases in Asia confirms a study from Thailand that found no incident KS case in 8034 HIV-infected children, even in the pre-cART era [30]. In contrast, a small record linkage study from Taiwan reported a KS incidence rate of 150/100 000 PYs in 230 HIV-infected children [4]. We found that the risk of developing

incident KS was lower in southern Africa compared with eastern Africa. This might be partly explained by lower HHV-8 prevalence in southern Africa than in eastern Africa [11, 12]. However, we cannot exclude that underreporting of incident KS, and limited generalizability of our results contributed to this finding. The number of prevalent KS cases in southern Africa was substantial and shows that many children in that region developed KS before initiating cART [31]. In our study, boys had a higher risk of developing KS than girls, which has not been shown consistently in previous studies [6, 9, 32, 33]. The overall KS incidence rate was highest soon after cART initiation and declined with time after cART initiation. This has not yet been described in children but is consistent with findings from previous studies in adults [6, 34]. The high KS incidence rate soon after cART initiation could be a result of unmasking immune reconstitution inflammatory syndrome KS [35, 36], reflect a slow increase in HHV-8–specific immune response over several months on cART [37], or represent the misclassification of prevalent KS cases as incident KS cases. Our KS incidence rate estimates are in line with results from previous studies done in the cART era (Supplementary Table 2) [2, 3, 5, 6]. However, KS incidence rates from different studies should be compared cautiously because of different study designs and settings.

Our study has shown that KS risk was considerable in HIV-infected children and adolescents who were born in or lived in SSA. This risk might be driven by high HHV-8 prevalence in these children [11–14] and barriers in access to healthcare [17–19]. We identified older age and advanced HIV/AIDS stage at cART initiation as risk factors for incident KS. The later children start cART, the longer their HIV infection goes untreated, increasing the risk of immunosuppression and subsequent KS. The risk for HHV-8 infection also increases with age [38, 39]. However, without patient-level data for HHV-8 serostatus, it was not possible to assess whether this contributed to the higher KS risk in older children. Programs for early testing and linkage to care for HIV-infected children still need improvement, especially for children in SSA and for children from SSA now living in Europe [16, 19]. WHO guidelines released in September 2015 recommend immediate cART initiation in all HIV-infected children regardless of immunodeficiency degree [40]. Timely implementation of this recommendation may reduce KS burden in at-risk children.

KS risk is substantial in HIV-infected children and adolescents of SSA origin, whether they live in SSA or Europe. Early cART initiation might reduce KS risk in these children.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

Acknowledgments:

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We thank Kali Tal for her editorial suggestions.

Financial support. Research reported in this publication was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (award U01AI069924; PI, Egger and Davies), the National Cancer Institute (supplement to 5U01AI069924-07), and the Swiss National Science Foundation (Ambizione-PROSPER PZ00P3_160407 to J. B.). The TREAT Asia Pediatric HIV Observational Database is an initiative of TREAT Asia, a program of amfAR, the Foundation for AIDS Research, with support from the US National Institutes of Health's National Institute of Allergy and Infectious Diseases, Eunice Kennedy Shriver National Institute of Child Health and Human Development, and National Cancer Institute as part of the International Epidemiologic Databases to Evaluate AIDS (IeDEA; U01AI069907), and the Austrian AIDS Life Association. The Kirby Institute is funded by the Australian Government Department of Health and Ageing and is affiliated with the Faculty of Medicine, the University of New South Wales. The COHERE study group has received unrestricted funding from Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS), France; HIV Monitoring Foundation, the Netherlands; and the Augustinus Foundation, Denmark. The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under EuroCoord (grant 260694). A list of the funders of the participating cohorts can be found at www.COHERE.org. The study sponsors had no role in the design of the study; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the paper for publication.

Potential conflicts of interest. M. Z. is a board member of Bern Cancer League and received support from the Swiss National Science Foundation, the World Cancer Research Fund, AstraZeneca, Aptalis, Dr Falk Pharma, GSK, Nestlé, Receptors Inc., and Regeneron. P. R. received support from ViiV. G. C. received support from Merck, Janssen, Gilead, Tibotec-Janssen, Roche, MSD, Boehringer Ingelheim, Bristol Myers Squibb, GSK, ViiV, Mylan, Abbvie, Abbott, Pfizer, and Lundbeck. M. D. received grants from the Centers for Disease Control and Prevention and the International AIDS Society. A. S. received grants from ViiV Healthcare for research, education, and community advocacy activities. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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APPENDIX

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