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Title: Kaposi Sarcoma Risk in HIV-Infected Children and Adolescents on Combination Antiretroviral Therapy from sub-Saharan Africa, Europe and Asia

Running title: KS risk in HIV-infected children on cART

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Key words: Kaposi sarcoma, HIV, children, antiretroviral therapy, cohort study

40-word summary: The risk of developing Kaposi sarcoma after starting combination antiretroviral therapy is substantial in HIV-infected children of sub-Saharan African origin, whether they live in Africa or Europe, but low in children of non-sub-Saharan African origin in Europe and in Asia.

Abstract (250 words, max. 250)

Background: The burden of Kaposi sarcoma (KS) in HIV-infected children and adolescents on combination antiretroviral therapy (cART) has not been estimated and 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 initiation of cART from 1996 onwards. We used Cox models to calculate hazard ratios (HR), adjusted for region and origin, sex, age at cART initiation, HIV/AIDS stage at cART initiation and cART start year.

Results: We included a total of 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 boys (adjusted HR 0.3, 95% CI 0.1-0.9), and increased with age (10-15 versus 0-4 years; adjusted HR 3.4; 95% CI 1.2-10.1) and advanced HIV/AIDS stage (CDC stage C versus A/B; adjusted HR 2.4; 95% CI 0.8-7.3) at cART initiation.

Conclusions: HIV-infected children and adolescents from SSA, but not those from other regions, have a high risk of developing KS after cART initiation. In these children early cART initiation might reduce KS risk.

Introduction

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 between 17 and 150 per 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 below six months in a recent trial from Malawi [10].

Immune deterioration following uncontrolled HIV replication increases the risk of developing KS in children co-infected 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 co-infection 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].

Combination ART 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- or 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 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 which 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 seven cART programs in South Africa, Zambia and Zimbabwe that collect KS data in children and adolescents systematically [20] or obtained 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 nine European countries (Austria, Denmark, France, Germany, Greece, Netherlands, Spain, the UK 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 <16 years of age 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) and among those in Europe, 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 WHO 2007 growth reference standards to calculate sex-standardized weight-for-age z-scores (WAZ) at cART initiation for children <10 years at 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 seven days after cART initiation. Children <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 three antiretroviral (ARV) drugs from any

class, including protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), and non-nucleoside 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 person-years 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, i.e., 0-3 months, 4-6 months, 7-12 months, 13-36 months, and >36 months. We ignored interruptions or 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 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 one year after cART initiation, and we restricted the analyses to children at increased risk of HHV-8 infection, i.e. those in Eastern and Southern Africa and children of SSA origin in Europe [11-13]. Results are presented as medians with interquartile ranges (IQR), 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, USA).

Results

Study population

The database included 35,133 HIV-infected children and adolescents. We excluded 3,321 because they did not initiate cART or had a missing cART start date. Another 6,821 children were excluded for reasons detailed in Figure 1. We excluded 53 children with prevalent KS; 26 from Eastern Africa, 22 from Southern Africa, three of SSA origin in Europe, and two from Asia. Children with prevalent KS were more often female than those with incident KS (43% versus 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, Zambia); Southern Africa (South Africa); Europe (Denmark, France, Germany, Ireland, Netherlands, Spain, and the UK); and Asia (Cambodia, India, Indonesia, Malaysia, Thailand, Vietnam). Most children included in Eastern Africa were located in Zambia (91%, n=10,173); in Europe the majority came from the UK and Ireland (63%, n=1,005) and in Asia, 43% (n=1,325) 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% versus 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, 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 below the age of 10 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, but for 21% (n=5,314) we could not determine the degree of immunosuppression at cART initiation. Children with missing CD4 data were younger than those for whom data were available (median age: 3.5 years versus 5.5 years), but the proportion with advanced CDC stage C was similar (9% versus 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 Eastern Africa (1.6 years). At the end of follow-up, median age ranged between 7.0 years in 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, three in Southern Africa, and three 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 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 three 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 three months after cART initiation. These early KS cases had initiated cART with lower median CD4 cell counts than children diagnosed with KS more than three months after cART initiation (90 cells/µl versus 310 cells/µl). None of the children who developed KS were diagnosed with Non-Hodgkin's Lymphoma before or after KS diagnosis.

In univariable analysis, KS risk was higher in European children of SSA origin compared to those in Eastern Africa (crude HR 1.8, 95% CI 0.5-6.1), see Table 2. However, the risk became similar (adjusted HR 1.0, 95% CI 0.2-6.4) after adjusting for sex, calendar period of cART initiation, age, and CDC stage at cART initiation. KS risk was lower in Southern than in Eastern Africa (adjusted HR 0.1, 95% CI 0.0-0.6), and increased with age at cART initiation (10-15 years versus 0-4 years, adjusted HR 3.4, 95% CI 1.2-10.1) and advanced CDC stage at cART initiation (C versus A/B, adjusted HR 2.4, 95% CI 0.8-7.3). KS risk was lower in girls than boys (adjusted HR 0.3, 95% CI 0.1-0.9). 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 co-infection, i.e. 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 one year after cART initiation, KS incidence rates per 100,000 pys were 162 in Eastern Africa, 39 in 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 S1). However, crude and adjusted HRs for developing KS did not change much compared to the main analysis (Supplementary Table S1).

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 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 papers looked into overall cancers in HIV-infected children, and did not have sufficient cases for a KS-specific analysis [2,3]. Some of the children from Eastern and Southern Africa were included in previous studies though [5,6]. Several limitations 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 under-estimation 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, which even in the pre-cART era found no incident KS case in 8,034 HIV-infected children [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 to Eastern Africa. This might be partly explained by lower HHV-8 prevalence in Southern Africa than 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 Southern Africa 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 since cART initiation. This has not yet been described in children but is consistent with findings from previous studies in adults [6,28,34]. 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 S2) [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 or lived in SSA. This risk might be driven by high HHV-8 prevalence in these children [11–14], and barriers in access to health care [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 in SSA and in 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.

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Tables and Figures

Table 1: Characteristics of included children and adolescents.

	Eastern Africa	Southern Africa	Europe, SSA origin	Europe, Non-SSA origin	Asia
	N (%)	N (%)	N (%)	N (%)	N (%)
All children	11,163 (100%)	9,174 (100%)	658 (100%)	934 (100%)	3,062 (100%)
Median follow-up time (IQR) [years]	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	5,547 (50%)	4,582 (50%)	335 (51%)	454 (49%)	1,569 (51%)
Girls	5,616 (50%)	4,592 (50%)	323 (49%)	480 (51%)	1,493 (49%)
Median age at cART initiation (IQR) [years]	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 [years]					
0-4	4,834 (43%)	5,551 (61%)	163 (25%)	545 (58%)	1,316 (43%)
5-9	3,344 (30%)	2,539 (28%)	219 (33%)	199 (21%)	1,205 (39%)
10-15	2,985 (27%)	1,084 (12%)	276 (42%)	190 (20%)	541 (18%)
Median weight for age z-score at cART initiation (IQR)ǂ	-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)
Weight for age z-score at cART initiation ǂ					
< -3	1,858 (23%)	1,343 (17%)	7 (2%)	27 (4%)	564 (22%)
-3 to <-2	1,733 (21%)	1,408 (17%)	22 (6%)	36 (5%)	513 (20%)
-2 to <-1	1,929 (24%)	1,795 (22%)	50 (13%)	88 (12%)	490 (19%)
≥ -1	1,774 (22%)	2,088 (26%)	193 (51%)	265 (36%)	419 (17%)
Missing	884 (11%)	1,456 (18%)	110 (29%)	328 (44%)	535 (21%)
First line cART regimen					
NNRTI-based	11,056 (99%)	4,980 (54%)	432 (66%)	434 (46%)	2,859 (93%)
PI-based	13 (<1%)	4,174 (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	4,958 (44%)	4,496 (49%)	215 (33%)	258 (28%)	1,433 (47%)
2008-2014	6,202 (56%)	4,442 (48%)	222 (34%)	192 (21%)	1,168 (38%)
CDC stage at cART initiation					
A/B	9,127 (82%)	8,029 (88%)	528 (80%)	701 (75%)	2,234 (73%)

C	925 (8%)	907 (10%)	65 (10%)	157 (17%)	370 (12%)
Missing	1,111 (10%)	238 (3%)	65 (10%)	76 (8%)	458 (15%)
Immunodeficiency at cART initiation*					
None/mild	1,754 (16%)	1,470 (16%)	156 (24%)	279 (30%)	331 (11%)
Advanced/severe	6,871 (62%)	5,672 (62%)	446 (68%)	473 (51%)	2,225 (73%)
Missing	2,538 (23%)	2,032 (22%)	56 (9%)	182 (19%)	506 (17%)
Median CD4 cell count at cART initiation (IQR) [cells/µl]**	241 (120-403)	265 (108-466)	259 (135-406)	290 (140-469)	118 (26-300)
CD4 cell count at cART initiation [cells/µl]**					
<200	2,272 (36%)	1,103 (30%)	172 (35%)	105 (27%)	940 (54%)
≥200	3,175 (50%)	1,734 (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%	2,139 (19%)	2,194 (24%)	168 (26%)	150 (16%)	1,353 (44%)
10-19%	3,206 (29%)	2,882 (31%)	260 (40%)	240 (26%)	807 (26%)
≥20%	1,617 (14%)	1,914 (21%)	148 (22%)	316 (34%)	373 (12%)
Missing	4,201 (38%)	2,184 (24%)	82 (12%)	228 (24%)	529 (17%)

cART, combination antiretroviral therapy; CDC, Centers for Disease Control and Prevention; IQR, interquartile range; KS, Kaposi sarcoma; NNRTI, non-nucleoside reverse-transcriptase inhibitors; PI, protease-inhibitors; SSA, sub-Saharan African.

ǂ Weight for age z-scores only calculated for children <10 years at time of measurement.

* WHO 2007 surveillance definition of immunodeficiency [26]

**Children younger than 5 years were excluded from the analysis of CD4 cell counts.

Table 2: KS incidence rates per 100,000 person-years and HRs for developing KS in children and adolescents who initiated cART.

	Patients (N)	Person-years	Cases (N)	Incidence rate (95% CI)	Crude HR (95% CI)	Adjusted HR (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	9,174	26,337	3	11.4 (3.7-35.3)	0.2 (0.0-0.5)	0.1 (0.0-0.6)
Europe, SSA origin	658	3,694	3	81.2 (26.2-251.8)	1.8 (0.5-6.1)	1.0 (0.2-6.4)
Europe, non-SSA origin	934	7,428	0	0 (0-49.8)	-	-
Asia	3,062	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 (0.2-1.0)	0.3 (0.1-0.9)
Age at cART initiation [years]						
0-4	12,409	34,923	7	20.0 (9.6-42.0)	1.0	1.0
5-9	7,506	25,431	7	27.5 (13.1-57.7)	1.5 (0.5-4.2)	1.2 (0.4-4.3)
10-15	5,076	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 ǂ						
< -3	3,799	9,709	0	0 (0-38.1)	-	-
-3 to <-2	3,712	10,408	2	19.2 (4.8-76.8)	1.4 (0.2-9.6)	-
-2 to <-1	4,352	12,870	7	54.4 (25.9-114.1)	3.9 (0.8-19.0)	-
≥ -1	4,739	15,817	2	12.6 (3.2-50.6)	1.0	-
Missing	3,313	11,550	3	-	-	-
First line cART regimen						
NNRTI-based	19,761	57,502	25	43.5 (29.4-64.3)	1.0	-
PI-based	4,998	15,945	1	6.3 (0.9-44.5)	0.2 (0.0-1.2)	-
Other cART	232	1,009	0	-	-	-
Year of cART initiation						
1996-2003	1,405	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 (0.3-5.5)	0.4 (0.0-3.6)
2008-2014	12,226	18,084	6	33.2 (14.9-73.9)	0.5 (0.1-2.8)	0.2 (0.0-2.1)
CDC stage at cART initiation						
A/B	20,619	60,261	17	28.2 (17.5-45.4)	1.0	1.0

C	2,424	7,027	4	56.9 (21.4-151.7)	2.2 (0.7-6.6)	2.4 (0.8-7.3)
Missing	1,948	7,168	5	-	-	-
CD4 cell count at cART initiation [cells/µl]*						
<200	4,592	15,331	8	52.2 (26.1-104.3)	1.0	-
≥ 200	5,980	18,265	5	27.4 (11.4-65.8)	0.5 (0.2-1.5)	-
Missing	2,010	5,937	6	-	-	-
CD4% at cART initiation						
<10%	6,004	20,563	7	34.0 (16.2-71.4)	1.0	-
10-19%	7,395	22,032	3	13.6 (4.4-42.2)	0.4 (0.1-1.4)	-
≥20%	4,368	12,003	2	16.7 (4.2-66.6)	0.4 (0.1-2.1)	-
Missing	7,224	19,858	14	-	-	-

cART, combination antiretroviral therapy; CDC, Centers for Disease Control and Prevention; CI, confidence interval; HR, hazard ratio; NNRTI, non-nucleoside reverse-transcriptase inhibitors; PI, protease-inhibitors; SSA, sub-Saharan African.

ǂ Weight for age z-scores only calculated for children younger than 10 years at time of measurement.

* Children younger than 5 years were excluded from the analysis of CD4 cell counts.

ᵠ Adjusted for region and origin, gender, age, year of ART initiation, and CDC stage at cART initiation.

Number of children and adolescents included in multivariable model: N = 23,043

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

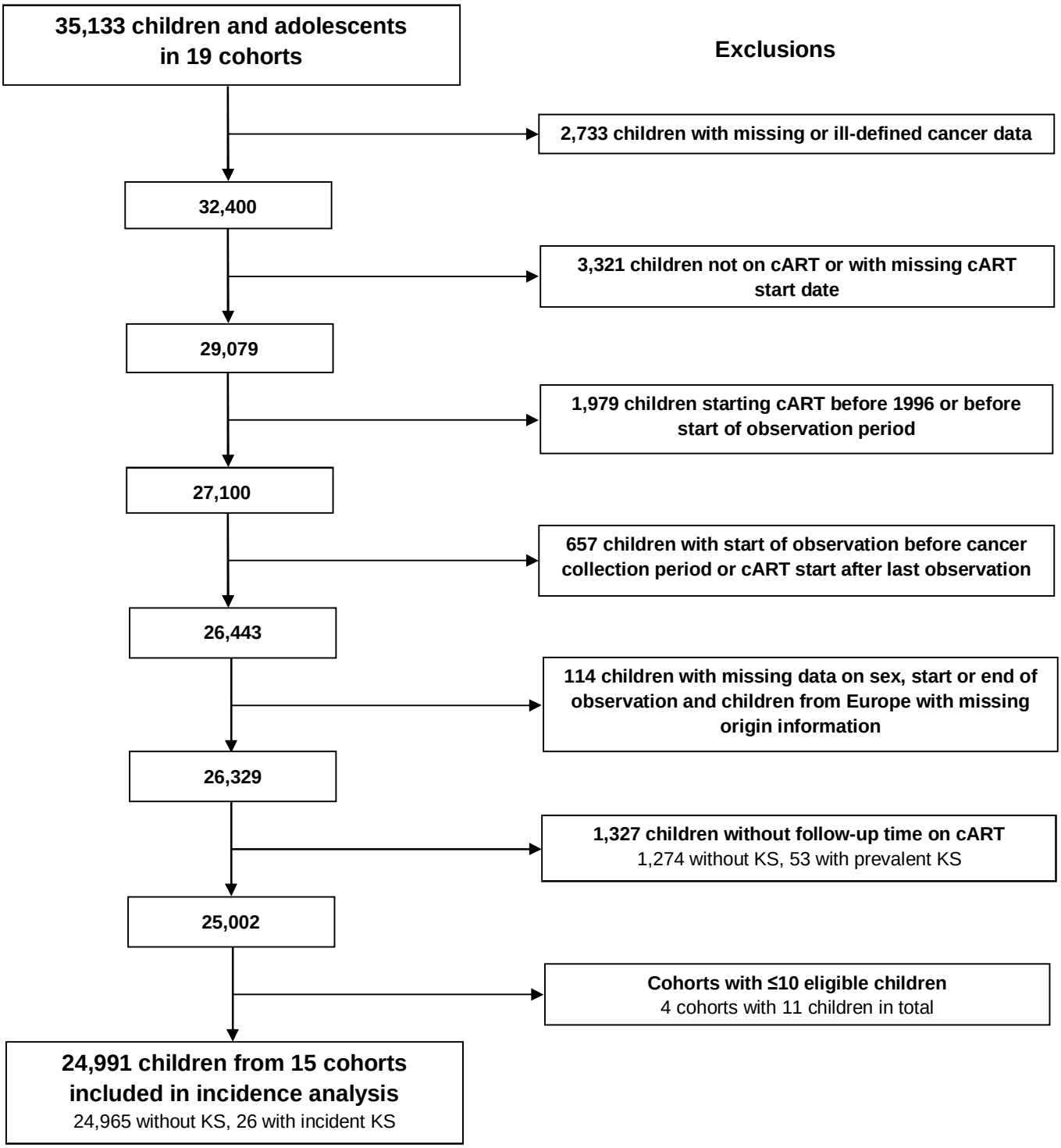
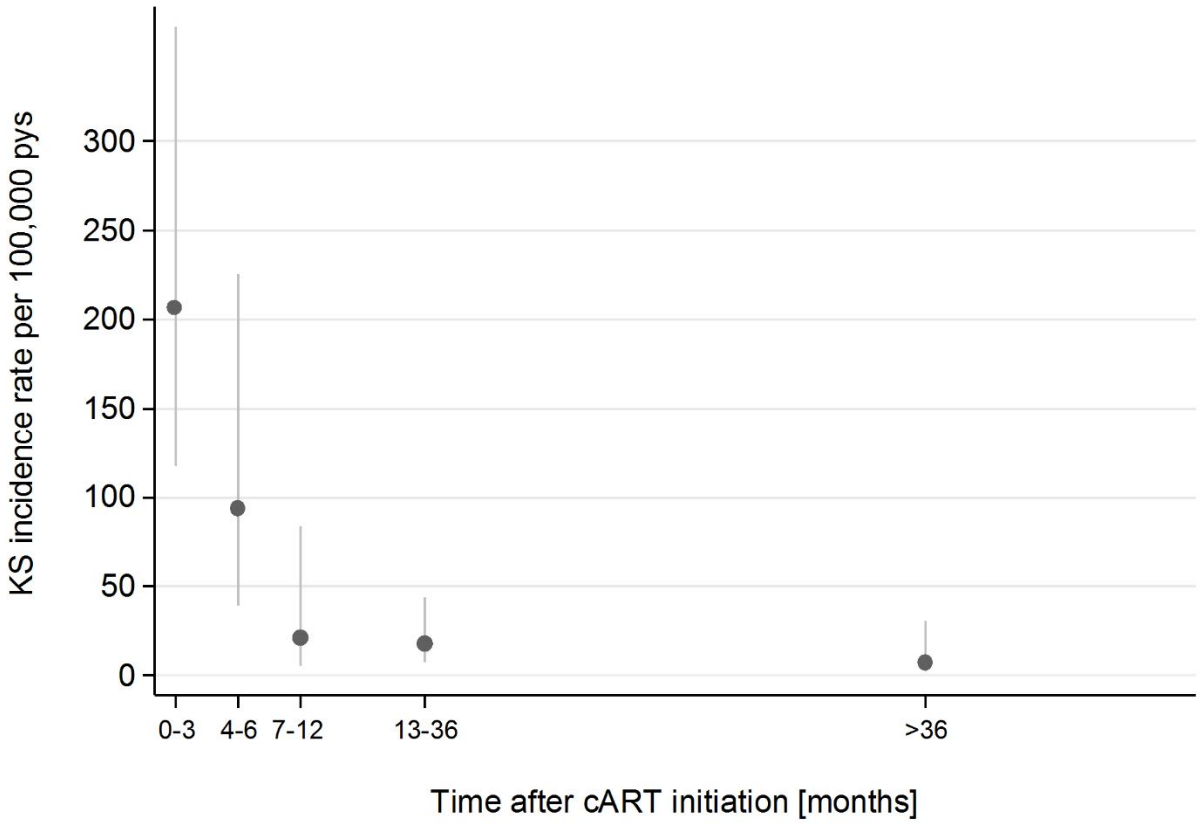


Figure 2: KS incidence rates in HIV-infected children and adolescents by time after cART initiation.



cART, combination antiretroviral therapy; KS, Kaposi sarcoma; pys, person-years.

Appendix: Supplementary Material

- **Table S1:** Sensitivity analyses with follow-up time restricted to 1 year after cART initiation: KS incidence rates per 100,000 person-years and HRs for developing KS in children and adolescents who initiated cART.

- **Table S2:** Literature review of studies reporting KS incidence rates in HIV-infected children and adolescents in the cART era.

Table S1: Sensitivity analyses with follow-up time restricted to 1 year after cART initiation: KS incidence rates per 100,000 person-years and HRs for developing KS in children who initiated cART.

	Patients (N)	Person-years	Cases (N)	Incidence rate (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)*
Overall	24,991	20,648	19	92 (59-144)	-	-
Region and origin						
Eastern Africa	11,163	8,665	14	162 (96-273)	1.0	1.0
Southern Africa	9,174	7,648	3	39 (13-122)	0.2 (0.1-0.9)	0.1 (0.0-0.8)
Europe, SSA origin	658	625	2	320 (80-1280)	2.1 (0.5-9.4)	0.4 (0.0-7.4)
Europe, non-SSA origin	934	908	0	0 (0-407)	-	-
Asia	3,062	2,803	0	0 (0-132)	-	-
Sex						
Boys	12,487	10,324	14	136 (80-229)	1.0	1.0
Girls	12,504	10,324	5	48 (20-116)	0.4 (0.1-1.0)	0.3 (0.1-0.9)
Age at cART initiation [years]						
0-4	12,409	9,761	5	51 (21-123)	1.0	1.0
5-9	7,506	6,562	5	76 (32-183)	1.5 (0.4-5.3)	1.1 (0.2-4.8)
10-15	5,076	4,325	9	208 (108-400)	4.2 (1.4-12.4)	3.7 (1.1-12.6)
Weight for age z-score at cART initiation ǂ						
< -3	3,799	2,926	0	0 (0-126)	-	-
-3 to <-2	3,712	3,045	2	66 (16-263)	2.7 (0.2-29.3)	-
-2 to <-1	4,352	3,636	5	138 (57-330)	5.6 (0.7-47.7)	-
≥ -1	4,739	4,108	1	24 (3-173)	1.0	-
Missing	3,313	2,608	2	-	-	-
First line cART regimen						
NNRTI-based	19,761	16,452	18	109 (69-174)	1.0	-
PI-based	4,998	4,014	1	25 (4-177)	0.2 (0.0-1.7)	-
Other ART	232	181	0	-	-	-
Year of cART initiation						
1996-2003	1,405	1,360	2	147 (37-588)	1.0	1.0
2004-2007	11,360	10,239	11	107 (59-194)	0.7 (0.2-3.2)	0.1 (0.0-1.8)
2008-2014	12,226	9,049	6	66 (30-148)	0.4 (0.1-2.0)	0.1 (0.0-1.4)
CDC stage at cART initiation						
A/B	20,619	17,128	11	64 (36-116)	1.0	1.0
C	2,424	1,805	4	222 (83-590)	3.4 (1.1-10.5)	3.6 (1.1-11.6)
Missing	1,948	1,715	4	-	-	-

CD4 cell count at cART initiation [cells/µl]**						
<200	4,592	3,925	7	178 (85-374)	1.0	-
≥ 200	5,980	5,232	3	57 (18-178)	0.3 (0.1-1.2)	-
Missing	2,010	1,729	4	-	-	-
CD4% at cART initiation						
<10%	6,004	5,081	6	118 (53-263)	1.0	-
10-19%	7,395	6,145	2	33 (8-130)	0.3 (0.1-1.4)	-
≥20%	4,368	3,472	1	29 (4-204)	0.2 (0.0-2.0)	-
Missing	7,224	5,950	10	-	-	-

cART, combination antiretroviral therapy; CDC, Centers for Disease Control and Prevention; CI, confidence interval; HR, hazard ratio; KS, Kaposi sarcoma; NNRTI, non-nucleoside reverse-transcriptase inhibitors; PI, protease-inhibitors; SSA, sub-Saharan African.

ǂ Weight for age z-scores only calculated for children younger than 10 years at time of measurement.

* WHO 2007 surveillance definition of immunodeficiency [26]

** Children younger than 5 years were excluded from the analysis of CD4 cell counts.

ᵗ Adjusted for region and origin, gender, age, year of ART initiation, and CDC stage at cART initiation.

Number of children and adolescents included in multivariable model: N = 23,043

Table S2: Literature review of studies reporting KS incidence rates in HIV-infected children and adolescents in the cART era.

Author, year	Cohort/Study	Country	Calendar years	Children (N)	Incident KS cases (N)	KS incidence rate per 100,000 person-years
Chiappini et al. 2007 [2]	Italian Register for HIV Infection in Children	Italy	2000-2004	787	1	38
Simard et al. 2012 [3]	HIV/AIDS Cancer Match Study*	USA	1996-2007	1,370	3	17
Chen et al. 2015 [4]	NHIRD	Taiwan	1998-2009	230	2	150
Bohlius et al. 2016 [5]	IeDEA-SA	South Africa	2004-2011	11,707	10†	34
Rohner et al. 2014 [6]	IeDEA-SA	Botswana, South Africa, Zambia, Zimbabwe	2004-2011	13,249	16†	59**
Current analysis	IeDEA-SA COHERE in EuroCoord TApHOD	South Africa, Zambia, Zimbabwe Denmark, France, Germany, Netherlands, Spain, UK, Ireland Cambodia, India, Indonesia, Malaysia, Thailand, Vietnam	1996-2014	25,033	26†	35**

* included children and adolescents diagnosed with AIDS only; † Three KS cases from Bohlius et al. 2016 [5] and 14 KS cases from Rohner et al. 2014 [6] were included in the current analysis; ** included children and adolescents who initiated cART only

COHERE, Collaboration of Observational HIV Epidemiological Research in Europe; IeDEA-SA, International Epidemiologic Databases to Evaluate AIDS Southern Africa; NHIRD, National Health Insurance Research Database; TApHOD, TREAT Asia Pediatric HIV Observational Database; cART, combination antiretroviral therapy; KS, Kaposi sarcoma; N, number.