***Target Journal:*** *Clinical Infectious Diseases*

Word limit: 3,000; references: max. 40

Word count: 2,999; References: 40; Tables: 2 (+ 2 in web appendix); Figures: 2

**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

**Authors:** ThePediatricAIDS-defining Cancer Project Working Group for IeDEA Southern Africa, TApHOD and COHERE in EuroCoord\*

\*A list of the writing group members is provided in the acknowledgments.

**Corresponding author:** Dr. Julia Bohlius, Finkenhubelweg 11, 3012 Bern, Switzerland. Email: julia.bohlius@ispm.unibe.ch; Phone: 0041 31 631 3523, Fax: 0041 31 631 3520

**Alternate corresponding author:** Dr. Eliane Rohner, Finkenhubelweg 11, 3012 Bern, Switzerland. Email: eliane.rohner@ispm.unibe.ch; Phone: 0041 31 631 3518, Fax: 0041 31 631 3520

**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-infectedchildren 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 IeDEAAsia-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.

**Funding**

Research reported in this publication was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number U01AI069924 (PI: Egger and Davies), the National Cancer Institute (supplement to 5U01AI069924-07) and the Swiss National Science Foundation (Ambizione-PROSPER PZ00P3\_160407 to JB). 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 U.S. 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 agreement n° 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.

**Acknowledgements**

**Writing group:** Eliane Rohner, Kurt Schmidlin, Marcel Zwahlen, Rana Chakraborty, Gary Clifford, Niels Obel, Sophie Grabar, Annelies Verbon, Antoni Noguera-Julian, Ali Judd, Intira Jeannie Collins, Pablo Rojo, Norbert Brockmeyer, Maria Campbell, Geneviève Chene, Hans Prozesky, Brian Eley, D Cristina Stefan, Alan Davidson, Cleophas Chimbetete, Shobna Sawry, Mary-Ann Davies, Azar Kariminia, Ung Vibol, Annette Sohn, Matthias Egger, Julia Bohlius.

**IeDEA-SA Steering Group:** Frank Tanser, Africa Centre for Health and Population Studies, University of Kwazulu-Natal, Somkhele, South Africa; Michael Vinikoor, Centre for Infectious Disease Research in Zambia, Lusaka, Zambia; Eusebio Macete, Centro de Investigação em Saúde de Manhiça, Manhiça, Mozambique; Robin Wood, Desmond Tutu HIV Centre (Gugulethu and Masiphumelele clinics), Cape Town, South Africa; Kathryn Stinson, Khayelitsha ART Programme and Médecins Sans Frontières, Cape Town, South Africa; Daniela Garone, Khayelitsha ART Programme and Médecins Sans Frontières, Cape Town, South Africa; Geoffrey Fatti, Kheth’Impilo Programme, South Africa; Sam Phiri, Lighthouse Trust Clinic, Lilongwe, Malawi; Janet Giddy, McCord Hospital, Durban, South Africa; Cleophas Chimbetete, Newlands Clinic, Harare, Zimbabwe; Kennedy Malisita, Queen Elizabeth Hospital, Blantyre, Malawi; Brian Eley, Red Cross War Memorial Children’s Hospital and Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa; Christiane Fritz, SolidarMed SMART Programme, Lesotho; Michael Hobbins, SolidarMed SMART Programme, Pemba Region, Mozambique; Kamelia Kamenova, SolidarMed SMART Programme, Masvingo, Zimbabwe; Matthew Fox, Themba Lethu Clinic, Johannesburg, South Africa; Hans Prozesky, Tygerberg Academic Hospital, Cape Town, South Africa; Karl Technau, Empilweni Clinic, Rahima Moosa Mother and Child Hospital, Johannesburg, South Africa; Shobna Sawry, Harriet Shezi Children’s Clinic, Chris Hani Baragwanath Hospital, Soweto, South Africa.

**COHERE Steering Committee:** Robert Zangerle (AHIVCOS),Giota Touloumi (AMACS), Josiane Warszawski (ANRS CO1 EPF/ANRS CO11 OBSERVATOIRE EPF), Laurence Meyer (ANRS CO2 SEROCO), François Dabis (ANRS CO3 AQUITAINE), Murielle Mary Krause (ANRS CO4 FHDH), Jade Ghosn (ANRS CO6 PRIMO), Catherine Leport (ANRS CO8 COPILOTE), Linda Wittkop (ANRS CO13 HEPAVIH), Peter Reiss (ATHENA), Ferdinand Wit (ATHENA), Maria Prins (CASCADE), Heiner Bucher (CASCADE), Caroline Sabin (UK CHIC), Diana Gibb (CHIPS), Gerd Fätkenheuer (Cologne-Bonn), Julia Del Amo (CoRIS), Niels Obel (Danish HIV Cohort), Claire Thorne (ECS), Amanda Mocroft (EuroSIDA), Ole Kirk (EuroSIDA), Christoph Stephan (Frankfurt), Santiago Pérez-Hoyos (GEMES-Haemo), Osamah Hamouda (German ClinSurv), Barbara Bartmeyer (German ClinSurv), Nikoloz Chkhartishvili (Georgian National HIV/AIDS), Antoni Noguera-Julian (CORISPE-cat), Andrea Antinori (ICC), Antonella d’Arminio Monforte (ICONA), Norbert Brockmeyer (KOMPNET), Luis Prieto (Madrid PMTCT Cohort), Pablo Rojo (CORISPES-Madrid), Antoni Soriano-Arandes (NENEXP), Manuel Battegay (SHCS), Roger Kouyos, (SHCS), Cristina Mussini (Modena Cohort), Pat Tookey (NSHPC), Jordi Casabona (PISCIS), Jose M. Miró (PISCIS), Antonella Castagna (San Raffaele), Deborah Konopnick (St. Pierre Cohort), Tessa Goetghebuer (St Pierre Paediatric Cohort), Anders Sönnerborg (Swedish InfCare), Carlo Torti (Italian Master Cohort), Ramon Teira (VACH), Myriam Garrido (VACH), David Haerry (European AIDS Treatment Group).

**COHERE Executive Committee:** Stéphane De Wit (Chair, St. Pierre University Hospital), Jose M. Miró (PISCIS), Dominique Costagliola (FHDH), Antonella d’Arminio Monforte (ICONA), Antonella Castagna (San Raffaele), Julia del Amo (CoRIS), Amanda Mocroft (EuroSida), Dorthe Raben (Head, Copenhagen Regional Coordinating Centre), Geneviève Chêne (Head, Bordeaux Regional Coordinating Centre). Paediatric Cohort Representatives: Ali Judd, Pablo Rojo.

**COHERE Regional Coordinating Centres (RCC)**: Bordeaux RCC: Diana Barger, Christine Schwimmer, Monique Termote, Linda Wittkop; Copenhagen RCC: Maria Campbell, Casper Frederiksen, Nina Friis-Møller, Dorthe Raben.

**COHERE Project Leads and Statisticians**: Juan Berenguer, Julia Bohlius, Vincent Bouteloup, Heiner Bucher, Alessandro Cozzi-Lepri, François Dabis, Antonella d’Arminio Monforte, Mary-Anne Davies, Julia del Amo, Maria Dorrucci, David Dunn, Matthias Egger, Hansjakob Furrer, Marguerite Guiguet, Sophie Grabar, Ali Judd, Ole Kirk, Olivier Lambotte, Valériane Leroy, Sara Lodi, Sophie Matheron, Laurence Meyer, Jose M. Miró, Amanda Mocroft, Susana Monge, Fumiyo Nakagawa, Roger Paredes, Lars Peters, Andrew Phillips, Massimo Puoti, Michael Schomaker, Colette Smit, Jonathan Sterne, Rodolphe Thiebaut, Claire Thorne, Carlo Torti, Marc van der Valk, Linda Wittkop.

**The TREAT Asia Pediatric HIV Network:** PS Ly\*, V Khol, SM Sarun, National Centre for HIV/AIDS, Dermatology and STDs, Phnom Penh, Cambodia; VB UNG\*, National Pediatric Hospital and University of Health Sciences, Phnom Penh, Cambodia; J Tucker, New Hope for Cambodian Children, Phnom Penh, Cambodia; N Kumarasamy\*, S Saghayam, and E Chandrasekaran, YRGCARE Medical Centre, CART CRS, Chennai, India; DK Wati\*, LPP Atmikasari, and IY Malino, Sanglah Hospital, Udayana University, Bali, Indonesia; N Kurniati\*, and D Muktiarti, Cipto Mangunkusumo General Hospital, Jakarta, Indonesia; SM Fong\*†, M Lim, and F Daut, Hospital Likas, Kota Kinabalu, Malaysia; NK Nik Yusoff\*, and P Mohamad, Hospital Raja Perempuan Zainab II, Kelantan, Malaysia; KA Razali\*, TJ Mohamed, and NADR Mohammed, Pediatric Institute, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia; R Nallusamy\*, and KC Chan, Penang Hospital, Penang, Malaysia; T Sudjaritruk\*, V Sirisanthana, L Aurpibul, and P Oberdorfer, Department of Pediatrics, Faculty of Medicine, Chiang Mai University and Research Institute for Health Sciences, Chiang Mai, Thailand; R Hansudewechakul\*, S Denjanta, W Srisuk, and A Kongphonoi, Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand; P Lumbiganon\*‡, P Kosalaraksa, P Tharnprisan, and T Udomphanit, Division of Infectious Diseases, Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; G Jourdain, PHPT-IRD UMI 174 (Institut de recherche pour le développement and Chiang Mai University), Chiang Mai, Thailand; T Bunupuradah\*, T Puthanakit, W Prasitsuebsai, and W Chanthaweethip, HIV-NAT, The Thai Red Cross AIDS Research Centre, Bangkok, Thailand; K Chokephaibulkit\*, K Lapphra, W Phongsamart, and S Sricharoenchai, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; KH Truong\*, QT Du, and CH Nguyen, Children’s Hospital 1, Ho Chi Minh City, Vietnam; VC Do\*, TM Ha, and VT An Children’s Hospital 2, Ho Chi Minh City, Vietnam; LV Nguyen\*, DTK Khu, AN Pham, and LT Nguyen, National Hospital of Pediatrics, Hanoi, Vietnam; ON Le, Worldwide Orphans Foundation, Ho Chi Minh City, Vietnam; AH Sohn\* and C Sethaputra, TREAT Asia/amfAR -- The Foundation for AIDS Research, Bangkok, Thailand; DA Cooper, MG Law\*, and A Kariminia, The Kirby Institute, UNSW Australia, Sydney, Australia.

\* TApHOD Steering Committee member

‡ co-Chair

Reference List

1. Biggar RJ, Frisch M, Goedert JJ. Risk of cancer in children with AIDS. AIDS-Cancer Match Registry Study Group. JAMA **2000**; 284:205–209.

2. Chiappini E, Galli L, Tovo PA, et al. Cancer rates after year 2000 significantly decrease in children with perinatal HIV infection: a study by the Italian Register for HIV Infection in Children. J Clin Oncol **2007**; 25:97–101.

3. Simard EP, Shiels MS, Bhatia K, Engels EA. Long-term cancer risk among people diagnosed with AIDS during childhood. Cancer Epidemiol Biomarkers Prev. **2012**; 21:148–154.

4. Chen M, Jen IA, Chen YM. Nationwide Study of Cancer in HIV-Infected Taiwanese Children in 1998-2009. J Acquir. Defic.Syndr. **2015**; 69:e117–e118.

5. Bohlius J, Maxwell N, Spoerri A, et al. Incidence of AIDS-defining and other cancers in HIV-positive children in South Africa: Record linkage study. Pediatr.Infect Dis J **2016**; 35(6):e164-70

6. Rohner E, Valeri F, Maskew M, et al. Incidence rate of Kaposi sarcoma in HIV-infected patients on antiretroviral therapy in Southern Africa: a prospective multicohort study. J Acquir. Defic.Syndr. **2014**; 67:547–554.

7. Mbulaiteye SM, Katabira ET, Wabinga H, et al. Spectrum of cancers among HIV-infected persons in Africa: the Uganda AIDS-Cancer Registry Match Study. Int J Cancer **2006**; 118:985–990.

8. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from http://globocan.iarc.fr. Accessed: 08/12/2015.

9. Cox CM, El-Mallawany NK, Kabue M, et al. Clinical characteristics and outcomes of HIV-infected children diagnosed with Kaposi sarcoma in Malawi and Botswana. Pediatr.Blood Cancer **2013**; 60:1274–1280.

10. Chagaluka G, Stanley C, Banda K, et al. Kaposi’s sarcoma in children: an open randomised trial of vincristine, oral etoposide and a combination of vincristine and bleomycin. Eur J Cancer **2014**; 50:1472–1481.

11. Minhas V, Brayfield BP, Crabtree KL, Kankasa C, Mitchell CD, Wood C. Primary gamma-herpesviral infection in Zambian children. BMC Infect Dis **2010**; 10:115.

12. Malope BI, Pfeiffer RM, Mbisa G, et al. Transmission of Kaposi sarcoma-associated herpesvirus between mothers and children in a South African population. J Acquir. Defic.Syndr. **2007**; 44:351–355.

13. Feiterna-Sperling C, Königs C, Notheis G, et al. High seroprevalence of antibodies against Kaposi’s sarcoma-associated herpesvirus (KSHV) among HIV-1-infected children and adolescents in a non-endemic population. Med. Microbiol. Immunol. **2016**; [Epub ahead of print].

14. Ablashi D, Chatlynne L, Cooper H, et al. Seroprevalence of human herpesvirus-8 (HHV-8) in countries of Southeast Asia compared to the USA, the Caribbean and Africa. Br.J Cancer **1999**; 81:893–897.

15. Ayuthaya PI, Katano H, Inagi R, et al. The seroprevalence of human herpesvirus 8 infection in the Thai population. Southeast Asian J Trop.Med Public Heal. **2002**; 33:297–305.

16. Global Update on the Health Sector Response to HIV, 2014. World Health Organization, Geneva, Switzerland, July 2014. Available from http://www.who.int/hiv/pub/progressreports/update2014/en/. Accessed: 31/08/2015.

17. Koller M, Patel K, Chi BH, et al. Immunodeficiency in children starting antiretroviral therapy in low-, middle-, and high-income countries. J Acquir. Defic.Syndr. **2015**; 68:62–72.

18. Cohen S, van Bilsen WP, Smit C, et al. Country of birth does not influence long-term clinical, virologic, and immunological outcome of HIV-infected children living in the Netherlands: a cohort study comparing children born in the Netherlands with children born in Sub-Saharan Africa. J Acquir. Defic.Syndr. **2015**; 68:178–185.

19. Macassa E, Burgard M, Veber F, et al. Characteristics of HIV-infected children recently diagnosed in Paris, France. Eur J Pediatr. **2006**; 165:684–687.

20. Egger M, Ekouevi DK, Williams C, et al. Cohort Profile: the international epidemiological databases to evaluate AIDS (IeDEA) in sub-Saharan Africa. Int J Epidemiol **2012**; 41:1256–1264.

21. Kariminia A, Chokephaibulkit K, Pang J, et al. Cohort profile: the TREAT Asia pediatric HIV observational database. Int J Epidemiol **2011**; 40:15–24.

22. Chêne G, Phillips A, Costagliola D, et al. Cohort Profile: Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord. Int J Epidemiol **2016**; [in press].

23. Composition of macro geographical (continental) regions, geographical sub-regions, and selected economic and other groupings. United Nations Statistics Division, New York, USA, 2013. Available from http://unstats.un.org/unsd/methods/m49/m49regin.htm. Accessed: 31/08/2015.

24. The WHO Child Growth Standards. World Health Organization, Geneva, Switzerland, 2006. Available from http://www.who.int/childgrowth/en/. Accessed: 09/12/2015.

25. WHO Reference 2007. World Health Organization, Geneva, Switzerland, 2007. Available from http://www.who.int/growthref/en/. Accessed: 09/12/2015.

26. WHO Case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. World Health Organization, Geneva, Switzerland, 2007. Available from http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf. Accessed: 13/01/2016.

27. Schneider E, Whitmore S, Glynn KM, Dominguez K, Mitsch A, McKenna MT. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years--United States, 2008. MMWR Recomm Rep **2008**; 57:1–12.

28. Lacombe JM, Boue F, Grabar S, et al. Risk of Kaposi sarcoma during the first months on combination antiretroviral therapy. AIDS **2013**; 27:635–643.

29. Franceschi S, Maso LD, Rickenbach M, et al. Kaposi sarcoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. Br.J Cancer **2008**; 99:800–804.

30. Pancharoen C, Nuchprayoon I, Thisyakorn U, et al. Hospital-based epidemiologic survey of malignancies in children infected with human immunodeficiency virus in Thailand. Pediatr.Infect Dis J **2005**; 24:923–924.

31. Davidson A, Wainwright RD, Stones DK, et al. Malignancies in South African children with HIV. J. Pediatr. Hematol. Oncol. **2014**; 36:111–7.

32. Gantt S, Kakuru A, Wald A, et al. Clinical presentation and outcome of epidemic Kaposi sarcoma in Ugandan children. Pediatr.Blood Cancer **2010**; 54:670–674.

33. Serraino D, Franceschi S. Kaposi’s sarcoma in children with AIDS in Europe and the United States. Eur. J. Cancer **1996**; 32A:650–1.

34. Yanik EL, Napravnik S, Cole SR, et al. Incidence and timing of cancer in HIV-infected individuals following initiation of combination antiretroviral therapy. Clin Infect Dis **2013**; 57:756–764.

35. Letang E, Miro JM, Nhampossa T, et al. Incidence and predictors of immune reconstitution inflammatory syndrome in a rural area of Mozambique. PLoS One **2011**; 6:e16946.

36. Orikiiriza J, Bakeera-Kitaka S, Musiime V, Mworozi EA, Mugyenyi P, Boulware DR. The clinical pattern, prevalence, and factors associated with immune reconstitution inflammatory syndrome in Ugandan children. AIDS **2010**; 24:2009–17.

37. Bourboulia D, Aldam D, Lagos D, et al. Short- and long-term effects of highly active antiretroviral therapy on Kaposi sarcoma-associated herpesvirus immune responses and viraemia. AIDS **2004**; 18:485–93.

38. Wakeham K, Webb EL, Sebina I, et al. Risk factors for seropositivity to Kaposi sarcoma-associated herpesvirus among children in Uganda. J Acquir. Defic.Syndr. **2013**; 63:228–233.

39. Butler LM, Dorsey G, Hladik W, et al. Kaposi sarcoma-associated herpesvirus (KSHV) seroprevalence in population-based samples of African children: evidence for at least 2 patterns of KSHV transmission. J Infect Dis **2009**; 200:430–438.

40. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. World Health Organization, Geneva, Switzerland, September 2015. Available from http://who.int/hiv/pub/guidelines/earlyrelease-arv/en/. Accessed: 05/10/2015.

**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 WAZ at cART initiation (IQR)ⱡ** | -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 ⱡ** |  |  |  |  |  |
| < -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; WAZ, weight-for-age z-scores.

ⱡ 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)ᶧ** |
| **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) |
| **WAZ at cART initiation ⱡ** |  |  |  |  |  |  |
| < -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; WAZ, weight-for-age z-scores.

ⱡ 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.

ᶧ 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.

\\KARAJAN\iedea_linc\IeDEA_Science\SA-CANCER\MULTIREGIONAL\EROH\word\Children\Paper\Revision\Resubmission\Figure 1.tif

cART, combination antiretroviral therapy; KS, Kaposi sarcoma.

**Figure 2:** KS incidence rates with 95% confidence intervals in HIV-infected children and adolescents by time after cART initiation.

\\KARAJAN\iedea_linc\IeDEA_Science\SA-CANCER\MULTIREGIONAL\EROH\word\Children\Paper\Revision\Resubmission\Figure 2.tif

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

**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

**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)ᶧ** |
| **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) |
| **WAZ at cART initiation ⱡ** |  |  |  |  |  |  |
| < -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; WAZ, weight-for-age z-scores.

ⱡ 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.

ᶧ 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 = 23,0

**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.