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Incidence of AIDS-Defining and Other Cancers in HIV-Positive Children in South Africa: Record Linkage Study

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Abstract

Background—Little is known on the risk of cancer in HIV-positive children in sub-Saharan Africa. We examined incidence and risk factors of AIDS-defining and other cancers in pediatric antiretroviral therapy (ART) programs in South Africa.

Methods—We linked the records of five ART programs in Johannesburg and Cape Town to those of pediatric oncology units, based on name and surname, date of birth, folder and civil identification numbers. We calculated incidence rates and obtained hazard ratios (HR) with 95% confidence intervals (CI) from Cox regression models including ART, sex, age, and degree of immunodeficiency. Missing CD4 counts and CD4% were multiply imputed. Immunodeficiency was defined according to World Health Organization 2005 criteria.

Results—Data of 11,707 HIV-positive children were included in the analysis. During 29,348 person-years of follow-up 24 cancers were diagnosed, for an incidence rate of 82 per 100,000 person-years (95% CI 55-122). The most frequent cancers were Kaposi Sarcoma (34 per 100,000 person-years) and Non Hodgkin Lymphoma (31 per 100,000 person-years). The incidence of non AIDS-defining malignancies was 17 per 100,000. The risk of developing cancer was lower on ART (HR 0.29, 95%CI 0.09–0.86), and increased with age at enrolment (>10 versus <3 years: HR 7.3, 95% CI 2.2-24.6) and immunodeficiency at enrolment (advanced/severe versus no/mild: HR 3.5, 95%CI 1.1-12.0). The HR for the effect of ART from complete case analysis was similar but ceased to be statistically significant (p=0.078).

Conclusions—Early HIV diagnosis and linkage to care, with start of ART before advanced immunodeficiency develops, may substantially reduce the burden of cancer in HIV-positive children in South Africa and elsewhere.

Keywords

cancer epidemiology; HIV/IADS; cohort study; record linkage

INTRODUCTION

South Africa is one of the countries most heavily affected by the HIV epidemic. An estimated 6.3 million people were living with HIV in South Africa in 2013, including 360,000 children.[1] HIV-positive children are at higher risk of developing cancer than children from the general population [2-4] or HIV-negative children.[5-8] Studies from Europe and the United States of America (USA) have shown that the incidence of cancer has declined as combination antiretroviral therapy (ART) has become more widely available.[3, 4, 9] Cohort studies of HIV-positive children are rare in the African region, and no study has so far assessed the impact of ART on the risk of developing cancer.[10] Moreover, data collection is often restricted to AIDS-defining cancers, i.e. Kaposi sarcoma (KS) and non-Hodgkin Lymphoma (NHL) in these cohorts.[11] Even the data on AIDS-defining cancers may be incomplete, since cohorts are based in ART programs but cancers are treated in

pediatric oncology units. Record linkages with cancer registries can overcome these limitations but to date only one record linkage study from the pre-ART era reported the incidence rate of cancer in HIV-positive children in an African setting.[12] Lastly, it may be difficult to estimate incidence and risk factors with precision because the number of HIV-positive children followed-up in any single cohort is typically small.

We did a record linkage study that combined data from five HIV cohort studies that participate in the International epidemiologic Databases to Evaluate AIDS (IeDEA) with the records of the four referral pediatric oncology units in South Africa. We aimed to define the incidence rate, risk factors and the impact of ART on the development of AIDS-defining and non AIDS-defining cancers in HIV-positive children who attended antiretroviral therapy (ART) programs in South Africa.

MATERIALS AND METHODS

Data sources

IeDEA is a research consortium established in 2006 to inform the scale-up of ART through clinical and epidemiological research.[11, 13-15] The four African regions of IeDEA have been described in detail elsewhere.[11] In this study, we included five South African treatment programs that provide care for HIV-positive children: the Khayelitsha Township ART program, the Tygerberg Hospital program and the Red Cross War Memorial Children's Hospital program in Cape Town; and the Harriet Shezi and Rahima Moosa programs in Johannesburg.[16] All five programs follow the guidelines of the South African National Department of Health[17,18] and have approval from their local ethics committee to provide data to IeDEA. Data are collected in the context of routine care at baseline and each follow-up visit, including socio-demographic data, the date of starting ART, type of treatment initiated, and CD4 measurements and HIV-1 plasma RNA levels.[11] The clinical and laboratory data are converted into a standardized format, the HIV Cohorts Data Exchange Protocol (HICDEP) and transferred to the IeDEA coordinating centers at the Centre for Infectious Disease Epidemiology and Research (CIDER), University of Cape Town, South Africa and the Institute of Social and Preventive Medicine (ISPM), University of Bern, Switzerland. The median date of the last follow up was August 19th 2010 (interquartile range 8 July 2008 to 2 June 2011).

Record linkage

HIV cohort data were linked with the records of four academic pediatric oncology referral units:[19] the Red Cross War Memorial Children's Hospital and the Tygerberg Hospital in Cape Town; and the Chris Hani Baragwanath and Charlotte Maxeke hospitals in Johannesburg. We included all HIV-positive children, aged 16 years or younger at enrolment, followed up at one of the five ART programs, and all patients with a confirmed cancer diagnosis and documented HIV-positive followed up at one of the four oncology units. We linked records probabilistically using the record linkage software G-Link of Statistics Canada,[20] based on folder numbers, South African civil identification numbers, date of birth, sex, name and surname, ethnicity, date of death, and date of cancer diagnoses. Based on probability weights, possible matches were identified and confirmed or rejected

after review. For each definite match, we retrieved data on the cancer diagnosis, including type, histology, date of diagnosis, stage and location and treatment. This information was anonymized and then incorporated into the IeDEA database.

Definitions

We defined the CD4 cell measurement at enrolment as the measurement closest to the enrolment date, within a window of 180 days before and 30 days after enrolment. We defined the CD4 measurement at start of ART as the measurement closest to the start of ART date, within a window of 180 days before and 30 days after ART was started. The degree of immunodeficiency (none, mild, advanced, severe) was defined using the WHO 2005 surveillance definition for the African region.[21]

We defined ART as a regimen of at least three antiretroviral drugs from at least two drug classes, including nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors. The calendar year of enrolment was categorized as before 2005 or thereafter. Calendar year of starting ART was categorized as before 2005, 2005 to 2009 and 2010 onwards to reflect the scale up of ART in 2005 and changes in the South African ART guidelines in 2010.[17,18] Prevalent cases were defined as cancers diagnosed before or at enrolment into the cohort. Incident cases were defined as cancers diagnosed during follow-up.

Statistical methods

In children not on ART, we measured time from the date of enrolment to the earliest of the date of diagnosis, start of ART, last follow-up visit or death. In children on ART, we measured time from the start of ART to the earliest of the date of the cancer diagnosis, last follow-up visit, or death. In children who were ART naïve at enrolment and who started ART during follow-up, we split the follow-up time so that they contributed time both to the not-on-ART and the on-ART analysis. We took an intent-to-continue-treatment approach and ignored changes to ART regimens, including interruptions and terminations. Incidence rates were calculated by dividing the number of children who developed cancer by the number of person-years at risk, with Poisson 95% confidence intervals (CI). We examined risk factors for incident cancer in Cox proportional hazard models stratified by cohort. Multivariable models were adjusted for time-updated ART, age at enrolment, sex, and degree of immunodeficiency (none, mild, advanced, severe) at enrolment. Missing CD4 counts and CD4% were multiply imputed using predictive mean matching and chained equations stratified by gender and age. In sensitivity analyses we restricted the analysis to the complete data and excluded patients with missing data.

Results are presented as medians with interquartile ranges (IQR), incidence rates per 100,000 person-years, Kaplan-Meier estimates of the cumulative incidence and crude and adjusted hazard ratios (HRs), with 95% CI. Stata version 13 (Stata Corporation, College Station, Texas, USA) was used for all statistical analyses.

RESULTS

The five ART cohorts included 12,448 eligible children (Table 1, Figure 1). Almost half of children (5,810, 47%) were from the Harriet Shezi ART program in Johannesburg. Most children (10,529, 85%) were enrolled in 2005 or later, at a time when ART was scaled up in South Africa. The majority of children (8,764, 70%) started ART at or after enrolment. CD4 cell measurements at enrolment were available for 7,995 (64%) children. Of these children, 5,333 (67%) presented with advanced or severe immunodeficiency (Table 1). The median CD4 cell count at enrolment was 493 cells/μL (IQR 216-922), the median CD4% was 15% (IQR 9%-23%). Among children with missing CD4 cell measurements, the imputed median CD4 cell count was 664 cells/μL (IQR 396-906) and the imputed median CD4% was 16% (IQR 13%-19%) at enrolment.

We identified a total of 71 eligible children with cancer: 49 (69%) were identified in the records of the oncology departments, 11 children (15%) were recorded with cancer in the ART programs, and 11 children (15%) were recorded in both data sets. Forty-seven children presented with cancer before or at enrolment, for a prevalence of 0.38% (95% CI 0.28-0.50), and 24 children developed cancer during follow-up. Children who presented with cancer or developed cancer later on were older at enrolment than children free of cancer: the median age at enrolment was 6.6 years and 5.0 years in children with prevalent and incident cancer, respectively, and 2.5 years in children not developing cancer. Children who developed cancer during follow-up were more likely to have experienced advanced or severe immunodeficiency than children who did not develop cancer (Table 1).

Table 2 shows the characteristics of patients with prevalent and incident cancer at the time of cancer diagnosis. Fifty-one percent of children presented with advanced or severe immunodeficiency at the time of cancer diagnosis; in 42% of children the CD4 measurements were missing. In children with available data the median CD4 cell count at diagnosis was 372 cells/μL (IQR 171-762) in children with prevalent cancer, and 599 cells/μL (IQR 62-978) in children with incident cancer. Most cancers were AIDS-defining, including 21 prevalent and 10 incident cases of KS, and 20 prevalent and 9 incident cases of NHL. Non AIDS-defining cancers included acute leukemias, Hodgkin lymphoma, nephroblastoma and leiomyosarcoma. Ninety percent of all cancers (64/71) were associated with Epstein Barr Virus (EBV) or HHV-8 co-infections (Kaposi sarcoma, lymphoma and leiomyosarcoma).

Cancer incidence and risk factors for developing cancer

The analyses of incidence were based on 11,707 children, of whom 24 developed cancer during 29348 person-years (Figure 1). The median observation time was 2.0 years (IQR 6 months-4.0 years). In the 24 children with incident cancer, the median time from enrolment into ART program to cancer diagnosis was 46 days (IQR 15-287). At the time of analysis, 6401 children (55%) were alive and under follow-up, 805 (7%) had died, 3,976 (34%) had been transferred to a different clinic, and 525 (4%) were lost to follow-up. In children on ART, the cancer incidence rate was 50/100,000 person-years (95% CI 29-89); in children not on ART, the rate was 220/100,000 person-years (95% CI 125-387) (Table 3). The incidence of AIDS-defining cancers was 65/100,000, with an incidence rate of 34/100,000 for KS, and

31/100,000 for NHL. The incidence of non AIDS-defining cancers was 17/100,000 person-years. The rate of cancer typically associated with EBV infection (NHL, Hodgkin lymphoma, leiomyosarcoma) was 34/100,000 person-years.

Table 4 presents the results from univariable and multivariable Cox models from the main analysis based on imputed CD4 data and the sensitivity analysis based on complete cases. The multivariable models were adjusted for immunodeficiency, age at enrolment, gender and time-updated ART use.

In the main analysis the multivariable model showed that children on ART had a lower risk of developing cancer than children not on ART (HR 0.29, 95% CI 0.09-0.86). Children with severe or advanced immunodeficiency at enrolment were more likely to develop cancer than children with mild or no immunodeficiency (HR 3.54, 95% CI 1.05-11.79). The risk of developing cancer increased with age at enrolment (HR children aged >10 years versus aged <3 years 7.33, 95% CI 2.19-24.57). The hazard ratios from the univariable model were similar but tended to have wider confidence intervals. The effect of ART on the risk of cancer was less pronounced and failed to reach statistical significance (HR 0.43, 95% CI 0.15-1.22). The hazard ratios from the analyses based on complete cases were similar to the analysis using multiply imputed data but the effect of ART on the risk of developing cancer was not statistically significant in this model (HR 0.23, 95% CI 0.04-1.18, Table 4).

DISCUSSION

This study shows that HIV-positive children in South Africa were at high risk of developing cancer with an overall incidence rate of 82/100,000 person-years. The majority of cancers were AIDS-defining with an incidence rate of 34/100,000 person-years for KS and 31/100,000 person-years for NHL. There were few non AIDS-defining malignancies with an incidence rate of 17/100,000 person-years. Children on ART had a substantially lower risk of developing cancer than children not on ART in multivariable analyses based on imputing data (HR 0.29, 95% CI 0.09-0.86). In complete case analysis the effect of ART was similar but not statistically significant. In all analyses the risk of developing cancer increased with age at enrolment.

This is the first study to describe the incidence rate of AIDS-defining and non AIDS-defining cancer and to estimate the impact of ART on the risk of developing cancer in HIV-positive children in South Africa. We used record linkage to identify both AIDS-defining and non AIDS-defining cancer cases, which are often not recorded, or only incompletely recorded in the data of HIV care and treatment programs. However, we may have missed cancer cases in children who were lost to follow-up or who sought treatment in other clinics. We identified only 24 incident cancer cases, and this limited our ability to conduct analyses stratified for different cancer types. Measurements of CD4 cell counts and percentages, HIV RNA loads, weight and height at enrolment into cohort were missing for a substantial proportion of patients. To overcome this limitation we used multiple imputation methods to impute missing CD4 cell measurements. This is a relatively young cohort (median age 2.5 years) most likely due to inclusion of many secondary and tertiary care sites where younger children and infants tend to be started on treatment. Given that we showed a strong

association between older age and incident malignancy, the burden of malignancy may be higher in cohorts of older children. Median time between enrolment and cancer diagnosis was short and we cannot exclude that some of the cancers classified as incident cancer were actually prevalent cancers which had not been diagnosed before enrolment.

Our study showed a cancer incidence rate of 69/100,000 person-years in HIV-positive children in the ART era (2005 or later), which is substantially higher than the Globocan 2012 cancer incidence rates in children aged < 14 years in South Africa (5/100,000 person-years), Europe (13/100,000 person-years), and the US (16/100,000 person-years).[22] Our incidence rates are lower than estimates from previous studies done in HIV-positive children in Europe and the US, see Table 5.[3, 4, 9] It is difficult to directly compare studies because of different study designs, settings and populations. The US AIDS cancer match study[2, 4] only included children diagnosed with AIDS, while the Italian HIV Registry[9, 23] and our study also included children with HIV that had not yet progressed to AIDS. The Italian HIV Registry study was predominantly based on children aged under one year [9] whereas the median age at enrolment was 2.5 years in our study and 6.3 years for the Pediatric AIDS Clinical Trials Group (PACTG) study.[3] The PACTG study relied on reporting of cancer within the cohort[3] whereas our and other studies included additional cases identified through record linkage with cancer registries.[2, 4] The definition of incident, as opposed to prevalent cancer case also differed across studies. The US AIDS cancer match study considered incident cancer cases to be those diagnosed three months after AIDS onset,[2, 4] but in our and other studies, any cancer recorded immediately after enrolment into cohort or registry was classified as an incident cancer.[3, 9, 23] More than 70% of all cancer cases identified in HIV-positive children in Europe and the US were EBV-associated cancer (i.e. NHL and leiomyosarcoma) while HHV-8 associated KS accounted for less than 8%.[3, 9] In contrast, in this South African study 46% of cancers were cancers that are typically associated with EBV, while 44% of all cancers were KS, which is typically associated with HHV-8.

Despite these differences several of our results are in line with the findings of the previous studies. Children who received ART were at substantially lower risk of developing cancer than children not on ART. This finding is consistent with the results of studies from high income countries,[3, 4, 9] see Table 5. Also, the risk of developing cancer tended to increase if immunodeficiency was more advanced at the time the child was enrolled into the cohort. This is in line with previous studies that showed that advanced stage HIV/AIDS disease,[3, 9] or CD4 cell percentages below 15% (severely immunosuppressed), increased the risk of developing cancer.[3]

Many cancer cases reported in our study were prevalent and detected at the time of enrolment into the program. Children with prevalent cancer presented late to the ART programs, at older ages and with severe or advanced immunodeficiency. Many of the prevalent cancers might have been prevented if the child had been enrolled into an ART program earlier. Indeed, early detection of HIV-infection, linkage to care and ART treatment may be crucial for preventing development of cancer in HIV-positive children in South Africa.[24-28] Since 2015 the World Health Organization guidelines recommend starting ART in all HIV-positive children regardless of age and immune status; 30 and South African guidelines recommend starting ART in children aged <5 years regardless of immune status

and at CD4 cell counts <500 cells/μL in children aged >5 years.[31] This recommendation should contribute to further reduce the risk of developing cancer in HIV-positive children. The reasons why children present late to ART programs need to be elucidated and uptake of ART increased. To better understand how best to prevent cancer in HIV-positive children in African settings we also need to investigate the impact of different first and second line ART regimens, and of different monitoring strategies (i.e. CD4 monitoring versus HIV viral load monitoring) on the risk of developing cancer.

In conclusion, our study linking data from HIV treatment and care programs with oncology clinic data suggests that early HIV diagnosis, linkage to care and start of ART before advanced immunodeficiency develops may substantially reduce the burden of cancer in HIV-positive children.

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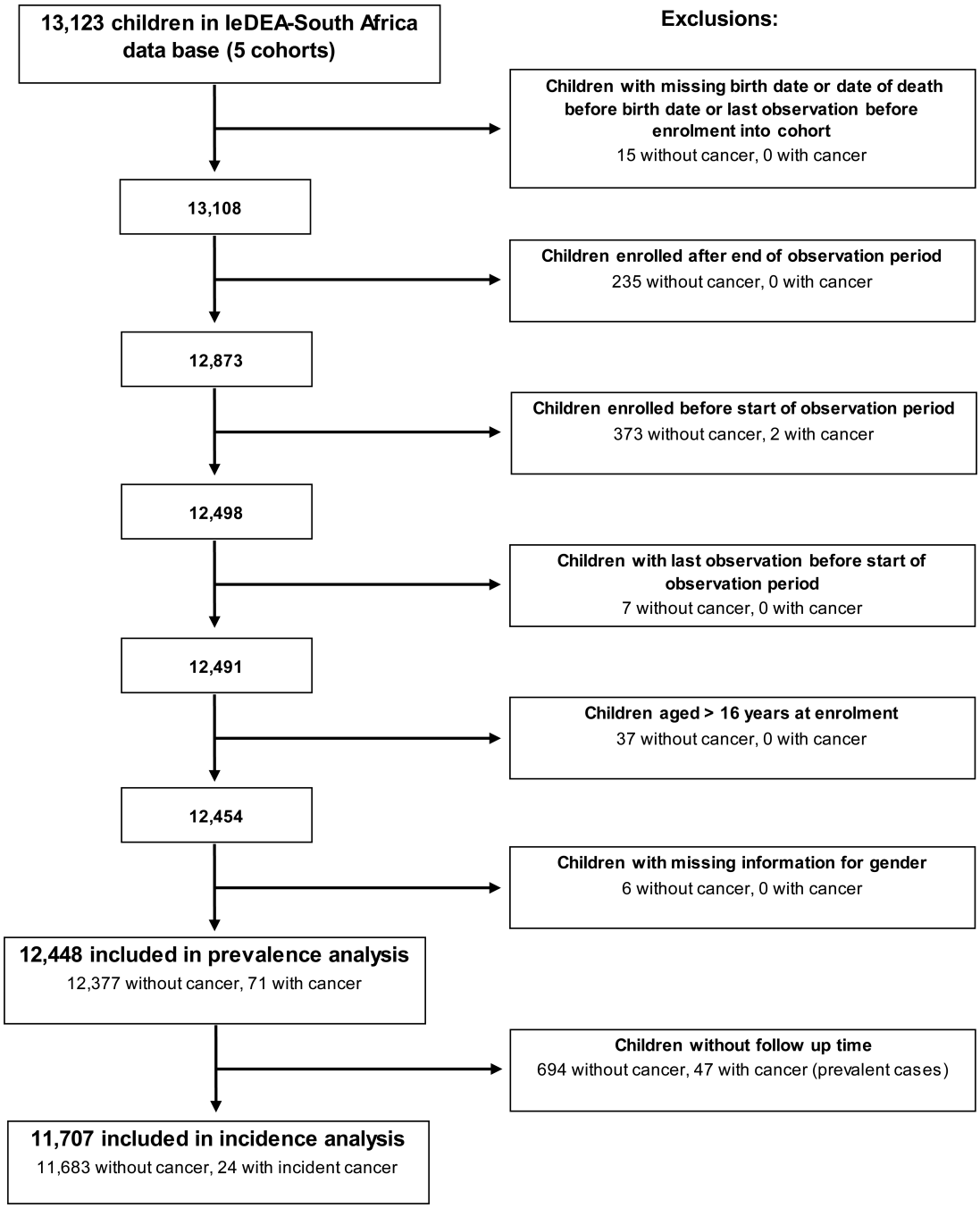

Figure 1.

Identification of study population for analysis of antiretroviral therapy and cancer in HIV-infected children in South Africa.

The flow diagram shows the number of included and excluded patients.

ART, antiretroviral therapy; IeDEA, International epidemiologic Databases to Evaluate AIDS

Table 1

Characteristics of HIV-positive children with prevalent and incident cancer in South Africa.

		Children with cancer		Children free from cancer
		Prevalent cases	Incident cases	
All patients		47	24	12,377
Cohort	Harriet Shezi	18 (38%)	7 (32%)	5,785 (46%)
	Khayelitsha	2 (4%)	1 (4%)	1,096 (9%)
	Rahima	1 (2%)	3 (16%)	2,752 (23%)
	Red Cross	20 (42%)	6 (24%)	1,664 (13%)
	Tygerberg	6 (15%)	7 (24%)	1,080 (9%)
Gender	Male	36 (77%)	14 (52%)	6,224 (50%)
	Female	11 (23%)	10 (48%)	6,153 (50%)
Age at enrolment	Median (IQR)	6.6 (4.3 – 9.9)	5.0 (2.5 – 9.0)	2.5 (0.7 – 6.3)
Age at enrolment	≤ 1 year	1 (2%)	2 (8%)	3,879 (31%)
	1 to < 3 years	3 (6%)	5 (21%)	2,857 (23%)
	3 to < 5 years	12 (26%)	5 (21%)	1,574 (13%)
	5 to < 10	20 (43%)	7 (30%)	2,897 (23%)
	≥ 10 years	11 (23%)	5 (21%)	1,170 (10%)
Immunodeficiency at enrolment *	No / mild	6 (13%)	2 (8%)	2,654 (21%)
	Advanced / severe	9 (20%)	9 (38%)	5,315 (43%)
	Missing	32 (68%)	13 (54%)	4,408 (36%)
Starting ART	Before enrolment	19 (40%)	2 (8%)	1,924 (16%)
	At or after enrolment	27 (57%)	20 (83%)	8,717 (70%)
	Never starting	1 (2%)	2 (8%)	1,713 (14%)
	Missing	0	0	23 (0.2%)
Calendar year of starting ART	Before 2005	11 (23%)	9 (38%)	1,213 (10%)
	≥ 2005 to	31(66%)	12 (50%)	7,628 (62%)
	≥ 2010	4 (9%)	1 (4%)	1,800 (15%)
	Never starting	1 (2%)	2 (8%)	1,713 (14%)
	Missing	0	0	23 (0.2%)
Calendar year of enrolment	Before 2005	10 (21%)	10 (42%)	1,899 (15%)
	≥ 2005	37 (79%)	14 (58%)	10,478 (85%)

ART, antiretroviral therapy

* WHO 2005 surveillance definition of immunodeficiency for the African region:[21] No significant immunosuppression: children up to age 12 months >35 CD4%; children 13 – 59 months >25 CD4%; children ≥ 5 years CD4 cell count > 500/mm3; Mild immunosuppression: children up to age 12 months 25-34 CD4%; children 13 – 59 months 20-24 CD4%; children ≥ 5 years CD4 cell count 350-499/mm3; Advanced immunosuppression: children up to age 12 months 20-24 CD4%; children 13 – 59 months 15-19 CD4%; children ≥ 5 years CD4 cell count 200-349/mm3; Severe immunosuppression: children up to age 12 months <20 CD4%; children 13 – 59 months < 15 CD4%; children ≥ 5 years CD4 cell count < 200/mm3.

Table 2

Characteristics at the time of cancer diagnosis of HIV-positive children with prevalent and incident cancer in South Africa.

		Children diagnosed with cancer	
		Prevalent cases	**Incident cases**
All patients		47	24
Age at cancer diagnosis	Median (IQR)	6.0 (3.7 – 9.7)	6.3 (3.8 – 10.2)
Age at cancer diagnosis	≤ 1 year	1 (2%)	1 (4%)
	1 to <3 years	6 (13%)	3 (13%)
	3 to <5 years	12 (26%)	3 (13%)
	5 to <10 years	18 (38%)	11 (46%)
	≥ 10 years	10 (21%)	6 (25%)
CD4 cell count at cancer diagnosis*	Median, IQR	372 (171 – 762)	599 (62 – 978)
Immunodeficiency at cancer diagnosis**	No / mild	3 (6%)	2 (8%)
	Advanced / severe	24 (51%)	12 (50%)
	Missing	20 (43%)	10 (42%)
ART history	Not on ART	43 (91%)	12 (50%)
	On ART	4 (8%)	12 (50%)
Type of cancer	HHV-8 associated, KS	21 (45%)	10 (42%)
	EBV associated	23 (49%)	10 (42%)
	NHL, Burkitt	9 (19%)	3 (13%)
	NHL, non Burkitt	10 (21%)	6 (25%)
	NHL, CNS lymphoma	1 (2%)	0
	Hodgkin lymphoma	3 (6%)	0
	Leiomyosarcoma	0	1 (4%)
	ALL, AML	0	4 (17%)
	Other***	3 (6%)	0 (0%)

ART, antiretroviral therapy; HHV-8, human herpes virus 8; EBV, Epstein-Barr virus; NHL, non Hodgkin lymphoma; ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia

*Based on 27 children with prevalent cancer and available CD4 count at cancer diagnosis, and 14 children with incident cancer and available CD4 count at cancer diagnosis.

**WHO 2005 surveillance definition of immunodeficiency for the African region:[21] No significant immunosuppression: children up to age 12 months >35 CD4%; children 13 – 59 months >25 CD4%; children ≥ 5 years CD4 cell count > 500/mm3; Mild immunosuppression: children up to age 12 months 25-34 CD4%; children 13 – 59 months 20-24 CD4%; children ≥ 5 years CD4 cell count 350-499/mm3; Advanced immunosuppression: children up to age 12 months 20-24 CD4%; children 13 – 59 months 15-19 CD4%; children ≥ 5 years CD4 cell count 200-349/mm3; Severe immunosuppression: children up to age 12 months <20 CD4%; children 13 – 59 months < 15 CD4%; children ≥ 5 years CD4 cell count < 200/mm3.

***Other: nephroblastoma, for two cases histology not provided

Table 3

Incidence rates of cancer per 100,000 person-years in HIV-positive children in South Africa.

	Person-years at risk	No. of cancer cases	Incidence rate (95% CI)
Any cancer	29,348	24	82 (55 – 122)
AIDS defining cancer			
Any	29,360	19	65 (41 – 102)
KS	29,373	10	34 (18 – 63)
NHL	29,393	9	31 (16 – 59)
Non AIDS defining cancer	29,393	5	17 (7 – 41)
Gender			
Male	14,919	14	94 (56 – 158)
Female	14,425	10	70 (37 – 129)
Age at enrolment			
≤ 1 year	6,343	2	32 (8 – 126)
1 to <3 years	7,362	5	68 (28 – 163)
3 to <5 years	4,908	5	102 (42 – 245)
5 to <10 years	8,197	7	85 (41 – 179)
≥ 10 years	2,534	5	197 (82 – 474)
Immunodeficiency at enrolment			
No / mild	6,282	2	32 (8 –127)
Advanced / severe	12,395	9	73 (38 – 140)
Missing	10,666	13	122 (71 -210)
ART treatment (time updated)			
Not on ART	5,464	12	220 (125 – 387)
On ART	23,864	12	50 (29 – 89)
Missing, unclear	16	0	-
Calendar year of starting ART			
Before 2005	5,197	9	173 (90 – 333)
≥ 2005 to 2009	20,627	12	58 (33 – 102)
≥ 2010	1,822	1	55 (8 – 390)
Missing / never starting	1,697	2	118 (30 – 471)
Calendar year of enrolment			
< 2005	9,012	10	111 (60 – 206)
≥ 2005	20,331	14	69 (41 – 116)

ART, antiretroviral therapy; KS, Kaposi Sarcoma; CI, confidence interval.

Table 4

Hazard ratios of developing cancer among HIV-positive children in South Africa

		Analysis based on imputed data (n=11,689)		Complete case analysis (n=7,646)	
		Univariable	Multivariable*	Univariable	Multivariable*
ART treatment (time updated)	Not on ART	1	1	1	1
	On ART	0.43 (0.15-1.22)	0.29 (0.09-0.86)	0.23 (0.04-1.20)	0.23 (0.04-1.18)
Gender	Male	1	1	1	1
	Female	0.74 (0.33-1.67)	0.69 (0.30-1.56)	0.88 (0.27-2.89)	0.86 (0.26-2.85)
Age at enrolment into ART program [years]	< 3 years	1	1	1	1
	3 to < 5 years	3.69 (1.15 – 11.84)	3.41 (1.06 – 10.97)	7.77 (1.27 – 47.34)	6.60 (1.08 – 40.44)
	5 to < 10 years	2.75 (0.95 – 7.97)	2.89 (1.00 – 8.36)	5.67 (1.01 – 31.81)	5.76 (1.02 – 32.46)
	≥ 10 years	7.05 (2.11 – 23.53)	7.33 (2.19 – 24.57)	8.41 (1.11 – 63.42)	8.29 (1.10 – 62.41)
Immunodeficiency at enrolment	No / mild	1	1	1	1
	Advanced / severe	2.59 (0.89 – 7.57)	3.54 (1.05 – 11.97)	1.87 (0.40 – 8.72)	2.22 (0.45 – 10.87)
Calendar year of starting ART	Before 2005	1	-	1	-
	≥ 2005 to 2009	0.45 (0.17 – 1.17)	-	0.45 (0.17 – 1.17)	-
	≥ 2010	0.26 (0.03 – 2.27)	-	0.26 (0.03 – 2.27)	-
Calendar year of enrolment	Before 2005	1	-	1	-
	≥ 2005	0.55 (0.22 – 1.35)	-	0.58 (0.15 – 2.84)	-

ART, antiretroviral therapy; CI, confidence interval.

All models were stratified by cohort.

Definition of immunodeficiency at enrolment into cohort according to WHO 2005 surveillance definition.

*Adjusted for time-updated ART, gender, age at enrolment and immunodeficiency at enrolment.

Table 5

Literature review: cancer incidence in HIV-positive children in low, middle and high income countries

Study	Country	Children included	Cancer cases identified	Cancer incidence rate per 100,000 pys (95% CI)		% reduction
				before ART era	during ART era	
British Paediatric Association Surveillance Unit[31]	UK	307	11 (7 NHL)	**1989-1995** NHL: 1,420	NA	NA
AIDS Cancer Match Study[2]	USA	4,954	124 * (36 incident in post AIDS period 4 – 27	**1980-1995:** 656	NA	NA
AIDS Cancer Match Study[4]	USA	5,850	106 *	**1980-1995:** 550	**1996-2007:** 213	61%
Pediatric AIDS Clinical Trials Group PACTG[3]	USA	2,969	37 (17 prevalent, 20 incident) **	**1993-1997:** 201 (0–414)	**1998-2003:** 139 (74–238)	31%
Italian Register HIV Infection in Children[23]	Italy	1,331	36	**1985-1999:** 418 (292–302)		NA
Italian Register HIV Infection in Children[9]	Italy	1,190	35	**1985-1995:** 449 (237–664)	**1996-1999:** 409 (168–650) **2000-2004:** 76 (0–180)	83%
Uganda Cancer Match Study[12]	Uganda	407	7, prevalent * 5, incident 2 (KS)	**1989-2002:** 160		NA
IeDEA-SA	South Africa	11,707	Total 71, prevalent 47, incident 24 **	**2000-2004:** 111 (60–206)	**2005-2011:** 69 (41–11)	38%

ADC AIDS-defining cancer; NADC non AIDS-defining cancer; KS Kaposi Sarcoma; NHL non Hodgkin Lymphoma; IeDEA-SA International Epidemiological Databases to Evaluate AIDS in Southern Africa; pys person years; NA not available.

* prevalent defined as: before or up to 3 months after AIDS, incident: later than 3 months after AIDS

** prevalent defined as: before cohort enrolment, incident: after cohort enrolment