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ORIGINAL ARTICLE

NON-AIDS DEFINING AND AIDS DEFINING MALIGNANCIES AND DETERMINANTS AMONG CHILDREN AND ADOLESCENTS LIVING WITH HIV IN ADDIS ABABA, ETHIOPIA

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ABSTRACT

Introduction: *The highest burden of human immunodeficiency virus (HIV) infection occurs in sub-Saharan Africa. Yet descriptions of oncologic disorders among children living with HIV in the region is limited. The objectives of this study were to describe the prevalence of Acquired immunodeficiency syndrome (AIDS) defining and non-AIDS defining malignancies among children and adolescents living with HIV and under care at a tertiary Hospital in Addis Ababa, Ethiopia.*

Methods: A facility based cross-sectional study was conducted from May 1 – September 30, 2019. There were 323 children and adolescents eligible for the study with their follow-up period spanning from 2000 – 2018. Data was collected using a structured and pre-tested questionnaire and analyzed using SPSS version 25.0 software. Bivariate and multivariate analyses were conducted with 95% confidence interval and P-value < 0.05.

Results: *The prevalence of all types of malignancies in the study population during their follow-up period was 3.4%: AIDS defining (1.55%) and non AIDS defining malignancies (1.85%). Non-Hodgkin's Lymphoma from the AIDS defining and Hodgkin's lymphoma among the non AIDS defining malignancies were the commonest diagnoses. Five of eleven patients achieved cure. Advanced HIV infection correlated significantly with a diagnosis of a malignancy (AOR: 7; 95% CI: 1.5, 34).*

Conclusions: *The prevalence of oncologic disorders in a pediatric cohort living with HIV is described. Advanced infection was associated with the development of malignancies. Early diagnosis and timely initiation of antiretroviral treatment can help prevent the development of cancers in children and adolescents living with HIV.*

Keywords: *HIV, children, adolescents, cancer, Ethiopia*

INTRODUCTION

The Human immunodeficiency virus (HIV) and its Acquired immunodeficiency syndrome (AIDS) were identified in the early 1980s (1). Globally, there were 1.7 million children living with HIV in 2020, of which 53% were on antiretroviral treatment (ART) (2). In Ethiopia, 58,000 children were living with HIV in the same year – only 21,300 of them were receiving ART (3).

Increased survival associated with antiretroviral drugs (ARVs) being more readily available has led to more non-communicable diseases being diagnosed in affected children. HIV-infected children have a higher risk of developing cancers compared to the general population (4). Most of such malignancies are linked with depletion of CD4+ lymphocytes, a loss of immune function and co-infections with oncogenic viruses like Epstein-Barr virus (EBV), Human herpes virus type 8 (HHV-8) and Human Papilloma virus (HPV) (5).

Equally, initiating early ART and immune reconstitution markedly decreases risk of oncologic diagnoses. Data from the Italian registry for HIV Infection confirms that about 449 per 100,000 ART naïve HIV-infected children develop some form of cancer annually while 76 per 100,000 per annum of children on ART do so. Similar benefits from ART were seen among HIV-infected children in the U.S. on therapy for more than two years (6,7).

Kaposi Sarcoma (KS) (1981), non-Hodgkin's lymphoma (NHL) (1985) and Invasive cervical cancer (1992), were the earliest identified AIDS defining illnesses (8) while in subsequent years, various non-AIDS defining cancers have increasingly been identified (9).A multi-center report from pediatric cohorts under HIV care in South Africa showed an incidence of malignancies of 82 per 100,000 person-years during a 29,348 person-years of follow-up period. KS and NHL were the most common malignancies among these cohorts.

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An incidence of 17 per 100,000 was reported for non-AIDS defining malignancies (10). These findings were also backed by Rees et al's review of the epidemiology of KS and NHL among sub-Saharan African children (11). An increased incidence of childhood KS, NHL, nasopharyngeal carcinoma and rhabdomysarcoma also occurred simultaneously with the HIV epidemic in Zambia in the early 1990s (12).

The World Health Organization (WHO) lists the following malignancies as being AIDS defining: KS, Burkitt's Lymphoma (BL), Diffuse Large B Cell Lymphoma (DLBCL), Primary CNS lymphoma (PCNSL), other NHLs - Peripheral T Cell Lymphoma, Primary Effusion/Body Cavity Lymphoma, Polymorphic B cell Lymphoma, Plasmablastic Lymphoma of the Oral Cavity and Cervical cancer (13).

Few data exist on the epidemiology of malignancies in children and adolescents living with HIV in the second most populous African country – Ethiopia. A cohort study on predictors of hospitalization among Ethiopian children on ART showed two of 86 hospitalizations during the study period among 405 patients were to treat KS (14). Existing knowledge on non-AIDS defining malignancies (NADMs) comes from a handful of case reports (15). The objectives of this study were to determine the prevalence and characterization of AIDS-defining and non-AIDS defining malignancies among children and adolescents living with HIV and under care at a tertiary Hospital in Addis Ababa, Ethiopia.

MATERIALS AND METHODS

Study setting and period

The study was conducted from May 1 – September 30, 2019. The study site – the Tikur Anbessa Specialized Hospital in Addis Ababa – is the largest tertiary referral center in Ethiopia. It is a public hospital affiliated with the College of Health Sciences of the Addis Ababa University. Its pediatric infectious diseases' clinic provides care for 512 children and adolescents living with HIV. Its pediatric hematology/oncology unit is the main referral center for treatment of children with malignancies from all over Ethiopia. Until recently, it served as the only pediatric cancer treatment center in the country.

Study design

An institution based retrospective cross-sectional study was implemented using chart reviews to determine the prevalence of AIDS defining malignancies (ADMs) and non-ADMs in the study population.

Sample size

All children and adolescents (0 – 18 years) under HIV care in the clinic were considered for enrollment into the study. Since there are no baseline epidemiologic studies conducted in this topic in Ethiopia, we used the following formula to calculate a sample size of 384 - taking the reference p value as 0.5 (50%) and a margin of error of 5%.

$n = z^2 \times p \times (1 - p)/d^2$; $z = 1.96$, $p = 0.5$, $d = 0.05$

We then gave a 15% estimate for incomplete records, leaving a final sample size of 326 children and adolescents.

Data collection and quality control

A structured and pre-tested data collection tool was prepared using selected demographic and clinical variables extracted from chart reviews. Data collection tool was tested on 5% of the estimated sample size (n = 16). Trainings were given for data collectors (medical interns who have received comprehensive HIV care and treatment trainings during their clinical courses) on data collection. The sample population (n = 326) were recruited by enrolling the first two children and leaving out the record of the third child and repeating the sequence for the entire set.

The principal investigator checked the data for completeness once a week. Further quality checks were performed by structured checklist set as a reminder for data collectors at the completion of each data set; as well as during data analysis.

Statistical analysis

Data was cleared, coded and exported to the SPSS statistical software version 25 for analysis. Descriptive statistics were used to outline magnitude of the problem while bivariate and multivariate analysis were utilized to identify predictors of the primary outcome. A 95% CI and a p-value of less than 0.05 were set as threshold for statistical significance.

Ethical considerations

The study protocol was approved by the Research and Publications Committee of the Department of Pediatrics and child health, College of Health Sciences, Addis Ababa University. Anonymity was ensured as retrieved and analyzed data was devoid of names, telephone numbers and chart number of patients.

RESULTS

Demographic and clinical description of the study population

Three hundred twenty three participants were eligible for the study. The mean age of participants was 13.6 years (SD 3.4).

Males accounted for 52.9% (171) of the study population.

A diagnosis of HIV infection was made before five years of age for 61% (167) of children. All were receiving antiretroviral drugs (ARVs) (table 1).

Table 1: Socio-demographic characteristics of study participants

Variables	Category	Frequency (n = 323)	Percent
Sex	Female	152	47.1
	Male	171	52.9
Residence	Addis Ababa	286	88.5
	Outside Addis Ababa (Urban)	10	3.1
	Outside Addis Ababa (Urban)	27	8.4
Age category	Less than 5 years	11	3.4
	5 - 10 years	42	13.0
	11 - 14 years	109	33.7
	15 - 18 years	162	49.8
Age at diagnosis of HIV infection	Less than 5 years	197	61.0
	5 - 10 years	106	32.8
	11 - 14 years	20	6.2

Two-thirds of our cohort (69.7%) had CD4 counts of more than 350/mm^3 in their latest determinations while 140 (43.3%) had stage three and four WHO clinical stages.

The majority were on NNRTI-based ART during the study period. Fifty (15.5%) children and adolescents had had a failed first line ART regimen, of which half had virologic failure (table 2).

Table 2: Clinical characteristics of study participants

Variables	**Category**	**Frequency (n = 323)**	**Percent**
CD4 at initiation of ART (/ mm3)	Less than 200/mm3	53	16.4
	200 – 350/mm3	45	13.9
	350/mm3 and above	225	69.7
WHO clinical stage during study period	Stage I	69	21.4
	Stage II	114	35.3
	Stage III	78	24.1
	Stage IV	62	19.2
ART regimen study participants were taking during study period	NNRTI-based	284	87.9
	PI-based	39	12.1
Duration on ART	Less than 5 years	88	27.2
	5 years or more	235	72.8
Failed first line ART regimen	Yes	50	15.5
	No	273	84.5
Type of failure in those who have had a failed first line ART regimen (n = 50)	Virologic	25	
	Immunologic	5	
	Clinical	1	
	Combined	19	

Key: NNRTI - Non-nucleoside reverse transcriptase inhibitor; PI – Protease inhibitor

Epidemiology and determinants of malignancies in the study population

The prevalence of all types of malignancies was 3.4% - with a 1.85% prevalence for NADMs and a 1.53% prevalence for ADMs. The commonest clinical presentation in children and adolescents with an oncologic diagnosis was a body swelling. There were ADM diagnoses in five children, all being NHLs. Among NADMs, HL was the commonest (4/6). The time lapse following initiation of ART till diagnosis of an oncologic malignancy (ADM or NADM) was less than one year in 4/11 children. Five of eleven patients achieved cure for their malignancies while a further five died due to their cancers or chemotherapy related complications (table 3).

Table 3: Clinical characteristics of study participants with diagnosed cancers

Variables	Categories	Frequency (n = 11)
Presenting clinical feature for diagnosed cancers	Body swelling	9
	Bleeding tendencies	1
	Cough and difficulty of breathing	1
Type of cancers	ALL	1
	HL	4
	NHL	5
	RMS	1
Time lapse following initiation of ART till an oncologic diagnosis	Simultaneous diagnoses	3
	Less than 1 year	4
	1 – 5 years	2
	5 years and more	2
Outcome of treatment for cancers	Cure	5
	Ongoing treatment	1
	Death	5

Key: ALL - Acute lymphoblastic leukemia, HL – Hodgkin's Lymphoma, NHL – Non-Hodgkin's Lymphoma, RMS – Rhabdomyosarcoma

Following bivariate and multivariate analysis, advanced HIV infection (WHO clinical stages 3 and 4) were noted to correlate with a diagnosis of a cancer. Children and adolescents living with advanced HIV infection (stages 3 and 4) were seven times more likely to have an oncologic diagnosis than those with WHO clinical stages 1 and 2 (table 4).

Table 4: Multi-variate analysis of factors associated with oncologic diagnoses

Variables	Categories	Presence of cancer		COR (95% CI)	AOR (95% CI)	p-value
		Yes	No			
Sex	Female	2	150			
	Male	9	162	4.2 (1.5, 11.5)	4.4 (0.9, 21)	0.066
Duration on ART	Less than five years	4	145	0.64 (0.28,1.45)	0.5 (0.15, 2)	0.40
	Five years and more	7	216			
WHO clinical stage	Stages 1 & 2	2	181			
	Stages 3 & 4	9	131	6 (2.3, 17)	7 (1.5, 34)	0.015
Failed 1st line ART regimen	Yes	2	48	1.2 (0.4, 3.4)	1.1 (0.2, 5.2)	0.97
	No	9	264			

Key: AOR – Adjusted odds ratio, COR – Crude odds ratio, CI – Confidence interval

DISCUSSION

Our study showed that 3.4% of the children and adolescents receiving HIV treatment and care in the study hospital had or have a diagnosis of ADM or NADM during their follow-up period. This fares poorly in comparison to the 71 children (0.6%) which had a diagnosis of cancer among a cohort of 11,707 children in two South African pediatric HIV clinics (10). It is also twice that was reported by Mbulaiteye et al (7/407) from the Uganda AIDS-Cancer registry (16). The high prevalence may be due to the reason that Tikur Anbessa specialized hospital is the main treatment center for children with malignancies from all over Ethiopia and it remained the only unit to do so in the country till recently.

Among our study population, the most common identified NADM was HL while all of the ADMs were NHLs. No cases of KS were diagnosed. This was in contrast to a multi-center case-control study conducted in four sub-Saharan countries (Botswana, Malawi, Tanzania and Uganda) where 83.8% of the 451 malignancies among children living with HIV over a 13 year period were KS (17). NHLs were the second most common oncologic diagnosis in the aforementioned east and southern African reports. Differences in KS epidemiology can be attributed to the fact that ours was a single-center study with a smaller study population.

We also observed that the odds for having a diagnosis of a cancer were higher in advanced HIV infection (WHO stages 3 and 4). People with untreated and progressing HIV infection have chronic antigenic stimulation, inflammation and cytokine dysregulation leading to development of lymphomas and other ADMs (18).

Bohlius et al noted (among their cohorts in pediatric HIV clinics in Johannesburg and Cape Town, South Africa) that those initiated on ART before two years of age had a four to five times higher risk for developing cancers versus children aged 2 years and above at ART initiation. No such correlations were seen in our study (10).

Close to half of children who developed various cancers achieved cure after initiating treatment. Cancer mortality is high among children living with HIV in Africa. Median survival in children and adolescents living with HIV and diagnosed with KS was less than six months in a recent trial from Malawi (19). In Uganda, median survival in HIV-infected children with Burkitt lymphoma was less than a year (11.8 months) (20).

High mortality rates in sub-Saharan countries may be related to delayed presentations, inadequate diagnostic and therapeutic modalities. Davidson et al from the South African Children's Cancer Study Group analyzed 288 children living with HIV with malignancies and determined that more than 80% presented with advanced disease. Their overall survival was 33.7% while it was 57.8% for those who received ART and chemotherapy (21). The aforementioned diagnostic gap which also prevents monitoring of drug toxicities as well as deficiencies in the armamentarium of chemotherapeutic and antiretroviral drugs which may help overcome harmful drug-drug interactions also shortens patient survival (22).

Conclusions

This is the first study looking into the epidemiology of malignancies in children and adolescents living with HIV in Ethiopia. It shows a high prevalence of oncologic diagnoses in a pediatric cohort living with HIV at the country's largest tertiary referral hospital. Advanced infection predicted development of a malignancy in the study population. Our study is limited by a small sample size which reflects the small overall numbers of children living with HIV nationwide (total of 58,000 in the country; 1% of which are under follow-up at the study hospital). Further multi-center studies are required as more and more joint pediatric HIV and oncology clinics start their service in other referral hospitals in Ethiopia. Efforts to improve early diagnosis and timely initiation of anti-retroviral treatment help prevent the development of cancers in children and adolescents living with HIV.

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Conflict of interests

The authors declare they have no conflict interests.

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