

Impact of infection with human immunodeficiency virus-1 (HIV)  
on the risk of cancer among children in Malawi – preliminary  
findings.

Nora Mutalima<sup>1\*</sup>, Elizabeth Molyneux<sup>2</sup>, W Thomas Johnston<sup>1</sup>, Harold Jaffe<sup>3</sup>, Steve Kamiza<sup>4</sup>,  
Eric Borgstein<sup>5</sup>, Nyengo Mkandawire<sup>5</sup>, George Liomba<sup>4</sup>, Mkume Batumba<sup>6</sup>, Lucy M  
Carpenter<sup>3</sup>, Robert Newton<sup>1</sup>

1. Epidemiology and Genetics Unit, Department of Health Sciences, Seebohm Rowntree  
Building, Area 3, University of York, York YO10 5DD, UK

2. Department of Paediatrics, University of Malawi, College of Medicine, P/Bag 360  
Chichiri, Blantyre 3, Malawi

3. Department of Public Health, University of Oxford, Rosemary Rue Building, Old Road  
Campus, Roosevelt Drive, Headington, Oxford, OX3 7LF UK

4. Department of Histopathology, University of Malawi, College of Medicine, P/Bag 360  
Chichiri, Blantyre 3, Malawi

5. Department of Surgery, University of Malawi, College of Medicine, P/Bag 360  
Chichiri, Blantyre 3, Malawi

6. Department of Ophthalmology, University of Malawi, College of Medicine, P/Bag 360  
Chichiri, Blantyre 3, Malawi

\*Corresponding author

Email addresses:

NM: [nora.mutalima@egu.york.ac.uk](mailto:nora.mutalima@egu.york.ac.uk)

EM: [emolyneux@malawi.net](mailto:emolyneux@malawi.net)

WTJ: [Tom.Johnston@egu.york.ac.uk](mailto:Tom.Johnston@egu.york.ac.uk)

HJ: [harold.jaffe@dphpc.ox.ac.uk](mailto:harold.jaffe@dphpc.ox.ac.uk)

SK: [skamiza@medcol.mw](mailto:skamiza@medcol.mw)

EB: [eborg@malawi.net](mailto:eborg@malawi.net)

NM: [nmkandawire@surgery.medcol.mw](mailto:nmkandawire@surgery.medcol.mw)

GL: [nliomba@admin.medcol.mw](mailto:nliomba@admin.medcol.mw)

MB: [mbatumba@surgery.medcol.mw](mailto:mbatumba@surgery.medcol.mw)

LMC: [lucy.carpenter@nuffield.ox.ac.uk](mailto:lucy.carpenter@nuffield.ox.ac.uk)

RN: [rob.newton@egu.york.ac.uk](mailto:rob.newton@egu.york.ac.uk)

# **Abstract**

## **Background**

The impact of infection with HIV on the risk of cancer in children is uncertain, particularly for those living in sub-Saharan Africa. In an ongoing study in a paediatric oncology centre in Malawi, children (aged  $\leq 15$  years) with known or suspected cancers are being recruited and tested for HIV and their mothers or carers interviewed. This study reports findings for children recruited between 2005 and 2008.

## **Methods**

Only children with a confirmed cancer diagnosis were included. Odds ratios (OR) for being HIV positive were estimated for each cancer type (with adjustment for age ( $<5$  years,  $\geq 5$  years) and sex) using children with other cancers and non-malignant conditions as a comparison group (excluding the known HIV-associated cancers, Kaposi's sarcoma and lymphomas, as well as children with other haematological malignancies or with confirmed non-cancer diagnoses).

## **Results**

Of the 586 children recruited, 541 (92%) met the inclusion criteria and 525 (97%) were tested for HIV. Overall HIV seroprevalence was 10%. Infection with HIV was associated with Kaposi sarcoma (29 cases; OR=93.5, 95% CI 26.9 to 324.4) and with non-Burkitt, non-Hodgkin lymphoma (33 cases; OR=4.4, 95% CI 1.1 to 17.9) but not with Burkitt lymphoma (269 cases; OR=2.2, 95% CI 0.8 to 6.4).

## **Conclusions**

In this study, only Kaposi sarcoma and non-Burkitt, non-Hodgkin lymphoma were associated with HIV infection. The endemic form of Burkitt lymphoma, which is relatively frequent in Malawi, was not significantly associated with HIV. While the relatively small numbers of children with other cancers, together with possible limitations of diagnostic testing may limit our conclusions, the findings may suggest differences in the pathogenesis of HIV-related malignancies in different parts of the world.

## **Background**

People infected with HIV have been found to be at increased risk of developing certain cancers [1-5] including Kaposi sarcoma, non-Hodgkin lymphoma and conjunctival carcinoma [6]. To date, however, the majority of evidence has been based on studies of adults; the impact of infection with HIV on the risk of cancer in children is less certain. Studies in developed countries, have suggested approximately 2.5% of children infected with HIV will develop cancer, lower than the proportion seen among infected adults [3]. Cancers described as being associated with HIV in children include Kaposi sarcoma, non-Hodgkin lymphoma and leiomyosarcoma [3, 7, 8] but to date, there are few data from sub-Saharan Africa, where the majority of HIV infected children live. Here, we examine the association between HIV infection and cancer among children in Blantyre, Malawi.

## **Results**

Out of a total of 586 suspected cases of childhood cancer, 541 were recruited into the study. All children who did not have a documented diagnosis were excluded (n=27, 4.6%). Of the children included in the study, 284 (52%) were diagnosed with Burkitt lymphoma, 53 (10%) with nephroblastoma, 34 (6%) with Kaposi sarcoma, 36 (7%) with non-Burkitt non-Hodgkin lymphomas, 28 (5%) with rhabdomyosarcoma and 22 (4%) with retinoblastoma (Table 1).

Children diagnosed with other types of cancer and non-malignant conditions comprised 15% of the children included in the analysis (84 children). There were no children diagnosed with leiomyosarcoma.

There was a preponderance of male children in the sample (59% overall) and most children (69%) resided in rural regions of the country (Table 1). The majority of the children were diagnosed after their fifth birthday (65%), a pattern observed for most of the cancer groupings, except for those with nephroblastoma or retinoblastoma; 35 children had missing age data. Overall, 62% of the cases had laboratory confirmed diagnoses and 37% had the diagnosis made on clinical grounds alone. Ten percent of all children (n=54) tested positive for HIV, although HIV prevalence varied by cancer type, ranging from 0% among children with retinoblastoma and rhabdomyosarcoma to 77% (n=24) among children with Kaposi sarcoma. Of the 506 children whose age was known, 25 children were under 18 months, and all were HIV seronegative.

HIV was strongly and positively associated with Kaposi sarcoma (OR=93.5, 95% CI 26.9 to 324.4,  $p<0.001$ ) and positively associated with non-Burkitt non-Hodgkin lymphoma (OR=4.4, 95% CI 1.1 to 17.9,  $p=0.04$ ), but not with Burkitt lymphoma (OR=2.2, 95% CI 0.8 to 6.4,  $p=0.13$ ; Table 2). No other cancer site or type was significantly associated with HIV infection although to date, the numbers available for analysis remain small. None of the 8 leukaemia cases and only 1 of the 10 cases of Hodgkin lymphoma were HIV seropositive.

## **Discussion**

Relative to adults, there are few published analytical epidemiological studies of cancer in HIV infected children, particularly among those living in sub-Saharan Africa and the

spectrum of cancers affecting children may be different [4]. Unlike adults, the great majority of HIV-infected children acquire the virus in utero or in the first months of life when the immune system is at an early stage of development. The proportion of children with HIV infection who will go on to develop a malignancy is at present poorly defined [3]. This study, carried out in Malawi, has found clear evidence of positive associations between HIV infection and both Kaposi sarcoma and non-Burkitt non-Hodgkin lymphoma in children. In contrast, we found little evidence of an association with Burkitt lymphoma in African children, although the numbers of HIV infected cases was small.

While Kaposi sarcoma in Malawian children was relatively rare prior to the HIV epidemic [9], the number of cases has increased during the era of HIV [10-12]. In some sub-Saharan African countries, Kaposi sarcoma is now one of the most common cancers in children [13-20]. This increase is likely to reflect the prevalence of HIV, although it is also in an area with a high background prevalence of the underlying causal virus Kaposi's sarcoma-associated herpesvirus (KSHV) [21].

The increased risk for non-Burkitt non-Hodgkin lymphoma in association with HIV in Malawian children is of similar magnitude to that reported for adults in South Africa (OR= 5.0, 95% CI 2.7 to 9.5, based on 128 cases), Rwanda (OR= 12.6, 95% CI 2.2 to 54.4, based on 26 cases), and Uganda (OR= 6.2, 95% CI 1.9 to 19.9, based on 21 cases) [22-25]. In these studies, the relative risk of non-Hodgkin lymphoma associated with HIV infection is an order of magnitude lower than those reported from developed countries [1, 26]. The reasons for this difference are not clear. Possible explanations for the apparent lack of non-Hodgkin lymphoma among HIV infected people in Africa include under-ascertainment of the malignancy and competitive mortality from other HIV-associated illnesses. It is important to

acknowledge, however, that 41% of lymphomas in this study were diagnosed on clinical grounds alone. As these children may have had HIV-associated lymphadenopathy rather than a true malignancy, the relative risk for this group of malignancies may also have been overestimated.

A case-control study from Uganda was the first to report an association between Burkitt lymphoma and infection with HIV among children living in an area where the tumour is relatively frequent [23] (note: a small subset of preliminary data from this study previously reported no association [27]). In 1994, no cases of Burkitt lymphoma were found in 78 HIV positive children in Côte d'Ivoire[28], and no increase in the incidence of childhood Burkitt lymphoma after the onset of the HIV epidemic was noted in Zambia [16]. A preliminary analysis of data from Malawi, published in early 2008, identified an excess risk of Burkitt lymphoma – based on 11 HIV infected cases and 228 without HIV (OR= 12.4, 95% CI 1.3 to 116.2)[29]. In the updated analyses reported here, the odds ratio is lower and no longer statistically significant, although the adjusted prevalence of HIV is similar to that of non-Burkitt non-Hodgkin lymphoma. However, the number of HIV positive children with Burkitt lymphoma reported in the literature to date is small and there remains substantial uncertainty about the role of HIV (if any) in the aetiology of this common malignancy among children in parts of sub-Saharan Africa. Our results and those of other African studies contrast with those from Western populations, where adults and children with AIDS are at least 1,000 times more likely to develop Burkitt-type lymphoma than the general population [1, 23, 30, 31], probably reflecting different pathogenetic mechanisms.

The overall HIV seroprevalence of 10% found among children included in this analysis was as expected in a population of children admitted to hospital in Malawi [32], and is similar to

that seen in children with cancer in Uganda [23]. For some cancers the number of cases available at the time of writing, was too small to draw reliable conclusions. Our results are broadly in line with those reported elsewhere in Africa [9, 13, 23, 33-35], although data on cancer in HIV-infected children remains scant. In developed countries a positive association between HIV and leiomyosarcomas and primary brain lymphomas has been reported [3, 36-40]. Brain tumours are difficult to diagnose in developing countries, although 4 cases with cranial tumours were reported here (all HIV seronegative). We found no cases of leiomyosarcoma.

The results reported here are subject to the potential problems of incomplete diagnostic verification. Laboratory verification of cancer diagnosis by histology and cytology was available for 64% of all cancers. This proportion varied by cancer site; being higher if the tumour was easily accessible for biopsy. These results are typical of studies in developing countries, where laboratory services are limited and compares favourably with other cancer series reported from Africa [13, 14, 41]. On the other hand, our study had the advantage of a high ascertainment of HIV status among all children with cancer ( 97%), which was consistently high across all cancer types, in contrast to a previous review of childhood cancer in Malawi [13]. It is possible, however, that children with both cancer and HIV were likely to die before a diagnosis could be made, potentially biasing our findings.

## **Conclusions**

The impact of HIV on the risk of cancers other than Kaposi sarcoma and non-Burkitt non-Hodgkin lymphoma remains uncertain and is the subject of further research. As data accrue from Malawi and elsewhere, the impact of HIV on the risk of other cancer types among children should be clarified.

## **Methods**

### **Recruitment and data collection**

All children aged 15 years or younger with a provisional diagnosis of cancer admitted to the paediatric wards at Queen Elizabeth Hospital in Blantyre, Malawi, are recruited into a study of childhood cancer. Here we present findings for children recruited between July 2005 and March 2008. Children with eye malignancies are cared for on a separate mixed adult and children's ophthalmology ward, and recruitment for the ophthalmology patients was only carried out between July 2005 and July 2006. Preliminary clinical diagnoses of cancer were made by one investigator (EM) and confirmed by histology, cytology or other laboratory investigations where possible. All diagnoses were coded based on available information to the International Classification of Childhood Cancer, 3<sup>rd</sup> edition [42]. Five local nurses were employed and trained to recruit children and their mothers into this study and to administer standardized questionnaires. The parent or guardian of each child was approached and invited to participate in the study and provide written informed consent for their child to be included. All children seen in the paediatric oncology ward with suspected cancer were routinely tested for HIV infection using Determine HIV (Abbott Laboratories, Illinois, USA) as a screening test and Uni-Gold<sup>TM</sup> HIV (Trinity Biotech PLC, Ireland) as a confirmatory test, as used in other studies from Malawi [13, 29, 43]. Appropriately trained staff provided pre- and post-HIV test counselling. Ethical approval for the study was obtained from the Oxford Tropical Research Ethics Committee and the Malawian College of Medicine Research and Ethics Committee.

### **Statistical analyses**

Initial descriptive analyses retained groupings of cancer types with at least 20 children diagnosed. Cancer types with fewer than 20 cases were included in a single group called 'other tumours' (illustrated in Table 1). All children diagnosed with non-Burkitt non-Hodgkin

lymphomas (and unspecified lymphomas) were included in a single group called ‘other lymphomas’ (shown in Table 1). For assessing the risk of having a specific cancer associated with HIV infection, children diagnosed with nephroblastoma (Wilms tumour), retinoblastoma and rhabdomyosarcoma were included with the smaller diagnostic groups due to small numbers of HIV positive children with these specific cancer diagnoses (an aggregate group called ‘all other cancers’, as illustrated in Table 2). The ‘all other cancers’ group (n=164) and non-malignant diagnoses (n=23) were grouped together to form a ‘control’ or ‘baseline’ group (n=187) of which 164 children had complete age, sex and HIV status data. A series of unconditional logistic regression models of the risk of each cancer group (Burkitt lymphoma, Kaposi sarcoma and non-Burkitt, non-Hodgkin lymphomas) being associated with HIV infection was constructed by maximum likelihood, adjusting for the child’s age at diagnosis (under 5 years, and 5 years and over) and sex: the ‘baseline’ group was used as the controls for each logistic regression. The association between HIV status and the risk of being diagnosed with one of the other cancer types with more than 20 patients (nephroblastoma, rhabdomyosarcoma or retinoblastoma) was assessed by removing patients with the diagnosis of interest from the baseline group and comparing them to those patients remaining. Kaposi sarcoma and lymphomas, which are known to be associated with HIV, were excluded from the comparison group, as were all other haematological malignancies (leukaemia n=8, Hodgkin lymphoma n=10 and small round blue cell tumours n=4) because of possible diagnostic overlap with lymphomas [44-46].

## **List of abbreviations**

HIV (Human Immunodeficiency Virus), AIDS (Acquired Immunodeficiency Syndrome), OR (Odds ratio), CI (Confidence Interval), KSHV (Kaposi’s sarcoma-associated herpesvirus).

## **Competing interests**

The authors declare that they have no competing interests.

## **Authors' contributions**

NM, RN, EM and LMC conceived of the study, and participated in its design and coordination and helped to draft the manuscript. WTJ performed the statistical analysis. SK, EB, NM, GL, MB and HJ participated in drafting the manuscript.

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## **Tables**

**Table 1 - General characteristics of 541 children with cancer diagnosed in Blantyre, Malawi**

**Table 2 - The association between HIV infection and specific cancer types**

## **Additional files**

**Additional file 1 – General characteristics of 541 children with cancer diagnosed in Blantyre, Malawi.**

Table 2 –The association between HIV infection and specific cancer types <sup>†</sup> .			
Adjusted prevalence of HIV infection (%) <sup>‡</sup>			
	Estimate	95% CI*	
Burkitt lymphoma (n=269)	9.1	(6.0 to 13.2)	
Kaposi sarcoma (n=29)	81.8	(63.1 to 93.6)	
Non-Burkitt non-Hodgkin lymphoma (n=33)	8.9	(1.8 to 24.0)	
All other cancers (n=164)	3.5	(1.3 to 7.6)	
Odds ratio for having the specific cancer given HIV infection compared to baseline <sup>§</sup> group			
	Odds ratio	95% CI	p-value
Burkitt lymphoma (n=269)	2.24	(0.78 to 6.43)	0.132
Kaposi sarcoma (n=29)	93.45	(26.92 to 324.37)	<0.001
Non-Burkitt non-Hodgkin lymphoma (n=33)	4.41	(1.09-17.85)	0.038
<sup>†</sup> Individual logistic regression models of the risk of having a specific cancer based on HIV seroprevalence compared to the ‘all other cancers’ group were adjusted for age class and gender; patients diagnosed with nephroblastoma, retinoblastoma and rhabdomyosarcoma have been included in the all other cancers group; patients with missing age, gender or HIV status have been excluded. <sup>‡</sup> Prevalence standardised to a population 50% female and 50% over 5 years old *Exact binomial confidence limits <sup>§</sup> Baseline group includes ‘all other cancers’ and non-malignant conditions.			

## Additional files

File name - Table 1- General characteristics of 541 children with cancer diagnosed in Blantyre, Malawi.

File format - PDF (Adobe Acrobat)

Title of data - Table 1- General characteristics of 541 children with cancer diagnosed in Blantyre, Malawi.

Description of data – Contains Table 1 that describes general characteristics of children recruited.

**Additional files provided with this submission:**

Additional file 1: table 1 general characteristics of 541 children with cancer diag,  
93K

<http://www.infectagentscancer.com/imedia/7132430129969127/supp1.pdf>