

Cancer in Human Immunodeficiency Virus-Infected Children: A Case Series From the Children's Cancer Group and the National Cancer Institute

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Purpose: To describe the spectrum of malignancies in human immunodeficiency virus (HIV)-infected children and the clinical outcome of patients with these tumors.

Methods: We retrospectively surveyed the Children's Cancer Group (CCG) and the National Cancer Institute (NCI) for cases of cancer that occurred between July 1982 and February 1997 in children who were HIV seropositive before or at the time of cancer diagnosis. We used Kaplan-Meier survivorship curves, hazard function estimates, and Cox proportional hazards models to evaluate survival.

Results: Sixty-four children (39 boys, 25 girls) with 65 tumors were reported. Thirty-seven children (58%) acquired HIV infection vertically (median age at cancer diagnosis, 4.3 years); 22 children (34%) acquired HIV through transfusion of blood or blood products (median age at cancer diagnosis, 13.4 years). Forty-two children (65%) had non-Hodgkin's lymphoma (NHL). Eleven children (17%) had leiomyosarcomas (or leiomyomas), which are otherwise exceptionally rare in children.

Other malignancies included acute leukemia (five children), Kaposi's sarcoma (KS; three children), Hodgkin's disease (two children), vaginal carcinoma in situ (one child), and tracheal neuroendocrine carcinoma (one child). Median survival after NHL diagnosis was 6 months (range, 1 day to 89 months) and after leiomyosarcoma was 12 months (range, 10 days to 19 months). The average monthly death rate after NHL diagnosis was 12% in the first 6 months, which decreased to about 2% thereafter. In contrast, the monthly death rate after leiomyosarcoma diagnosis increased from 5% in the first 6 months to about 20% thereafter.

Conclusion: After NHL, leiomyosarcoma is the second leading cancer in children with HIV infection. Both cancers have high mortality rates; improved outcome for NHL, in particular, may depend on earlier diagnosis and therapy.

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PEDIATRIC HUMAN immunodeficiency virus (HIV) infection is a serious problem in the United States. It is estimated that more than 20,000 children are currently living with HIV infection.¹ Furthermore, children tend to progress more rapidly to AIDS than adults, with approximately 25% of infants who develop severe immunodeficiency during the first year of life.² Similar to children with congenital and other acquired immunodeficiencies, children with HIV infection are at higher risk of developing malignant neoplasms.³ It is possible that with prolonged survival because of recent improvements in antiretroviral therapy and supportive care, children with HIV infection will develop malignancies at an increased rate.

Of 7,629 children (aged younger than 13 years) with AIDS reported to the Centers for Disease Control and Prevention (CDC) as of December 1996, 156 children (2%) were known to have cancer: there were 50 children with Burkitt's lymphomas, 48 children with immunoblastic lymphomas, 30 children with CNS lymphomas, and 28 children with Kaposi's sarcomas (KS).⁴ Both adults and children with HIV infection have an increased incidence of non-Hodgkin's lymphoma (NHL). However, whereas KS is the AIDS indicator disease in approximately 15% of adults,⁵ it is the AIDS-defining condition for less than 2% of pediatric patients. This suggests that etiologic cofactors for HIV-related malignancies may differ between children and adults.

Although several approaches have been used to describe the epidemiology of HIV-related cancer in adults, little is known about the influence of HIV infection on pediatric malignancies. To determine the impact of HIV infection on pediatric cancer, we surveyed the experience of member institutions of the Children's Cancer Group (CCG) and that of the Pediatric Branch of the National Cancer Institute (NCI). CCG hospitals collectively diagnose and treat approximately half of the pediatric cancers in the United States.⁶ Our three major objectives were to define the spectrum of malignancies in HIV-infected children, describe the clinical outcome of patients with these tumors, and determine differences between adults and children with HIV infection and cancer.

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METHODS

Study Population

We surveyed the member institutions of the CCG and the Pediatric Branch of the NCI and asked principal investigators to report on any cases of children with both HIV infection and cancer. The CCG is the largest international organization devoted to research on cancer in children. It includes 116 pediatric medical centers in the United States, Canada, and Australia. A total of 84 CCG centers responded to our survey. The Pediatric HIV Branch is a division of the NCI, which serves as a national referral center and offers HIV-related treatment protocols. Children are referred by their primary care pediatricians and undergo screening evaluations to be eligible for protocol enrollment. All NCI cases described in this study were HIV-seropositive children followed up for treatment of HIV infection and its complications who subsequently developed cancer. Therefore, we were able to calculate person-years of observation for all HIV-seropositive children followed up by the NCI Pediatric Branch.

We collected the following information: demographics, dates of HIV and cancer diagnoses, degree of immunosuppression at the time of cancer diagnosis, treatment modalities and response, HIV transmission category, and outcome. Data were abstracted retrospectively from medical records and autopsy reports. To ensure confidentiality, each case was assigned a unique study number. Data collection was performed from August 1994 to February 1997. Because no personal identifiers were collected nor any patient interaction occurred, informed consent was not sought.

We defined cases as pediatric (less than 21 years of age) patients who were HIV-seropositive before or at the time of cancer diagnosis. To calculate latency (time from HIV infection to cancer diagnosis), the time of HIV seroconversion was estimated according to route of acquisition. We considered HIV seroconversion to be at birth both for vertically HIV-infected children and for children infected with HIV during a neonatal blood transfusion. For hemophiliacs, the precise date of HIV seroconversion was usually unknown. However, most hemophiliacs became infected during a relatively short period of time as indicated by analyses of the seroconversion dates of subjects in the Multicenter Hemophilia Cohort Study.⁷ Therefore, for purposes of estimating latency, we used a common seroconversion date of November 1981 (after the birth of all hemophiliac cases), the median date of seroconversion for moderate-dose factor VIII users.⁷ The variability of the common date would add or subtract approximately 1 year to our calculated latency because half of the hemophiliac subjects probably became HIV infected between September 1980 and October 1982.⁷ HIV seroconversion could not be estimated for five patients who acquired HIV by transfusion but were not hemophiliacs or neonates, nor for three cases of sexually transmitted HIV infection. Thirteen children had dates of HIV acquisition after cancer diagnosis and were excluded from the study.

Statistical Analysis

Follow-up time was determined from the time of initial visit until the time of last contact or time of death. Expected cancer incidence was then computed from cancer-specific incidence rates for the general pediatric population as determined by the Surveillance, Epidemiology, and End Results (SEER) Program.⁸ The relative risk of specific cancers among this population was estimated by using the standardized incidence ratio (SIR), the quotient of observed to expected cases. For leiomyosarcomas, the expected incidence in children was estimated by multiplying the age-specific soft tissue sarcoma rate in the general pediatric population (eight per million) by 2%, an estimate of the fraction of soft tissue sarcomas that were leiomyosarcomas.⁹

We considered the following variables in evaluating post-cancer diagnosis survival: age at the time of cancer diagnosis, mode of HIV transmission, prior AIDS diagnosis, and percent of total lymphocytes that are CD4+ T cells. CD4 percentage was used as a marker of the degree of immunosuppression because it did not need to be age adjusted and had less measurement variability than the absolute count.¹⁰ CD4 percentage at the time of cancer diagnosis was approximated by measurements performed up to 8 months before or 3 months after cancer was diagnosed.

Survival in the months after cancer diagnosis was estimated by the Kaplan-Meier product-limit method.¹¹ Cox proportional hazards models were used to examine the effect of selected variables on the mortality rate. For selected Kaplan-Meier curves, the corresponding monthly death rates (percent who died among patients still alive) were estimated by spline functions¹² to derive smooth estimates without making strong parametric assumptions.

RESULTS

Twenty-three of 84 responding CCG centers and the NCI reported 64 HIV-infected children with 65 tumors diagnosed between 1982 and 1997. One child with hemophilia and HIV infection developed a Burkitt's lymphoma of the nasopharynx at 12.6 years of age and a distinct large-cell lymphoma of the lung 19 months later. For children with vertically acquired HIV infection, cancer occurred at a median time of 4.3 years after HIV seroconversion compared with 10.4 years for children who acquired HIV infection by transfusion of contaminated blood or blood products. The demographic characteristics, HIV risk group, median ages of participants at cancer diagnosis, and latency times are listed in Table 1.

NHL accounted for 65% (42) of all tumors reported. Other tumors included 11 (17%) leiomyosarcomas/leiomyomas, four (6%) acute lymphoblastic leukemias, three (5%) KSSs, two (3%) Hodgkin's disease, one (2%) acute myeloid leukemia, one vaginal carcinoma in situ, and one tracheal carcinoma. Three of the leiomyomas and two NHLs have been described in previous reports.¹³⁻¹⁵

NHLs

Lymphoma was the initial AIDS-defining condition in 18 (43%) of the 42 cases. The overall median age at diagnosis was 5.5 years (range, 1.1 to 19.4 years).

The majority of the NHLs were high-grade B-cell tumors of immunoblastic/large-cell or small noncleaved cell histologies (Table 2). Extranodal disease occurred in more than 80% of the children, with the two most common sites the gastrointestinal (GI) tract (37%) and the CNS (17%). There were six primary CNS lymphomas, all of which were of large-cell histology and supratentorial location. Four of the primary CNS lymphomas were solitary lesions and two were multicentric. Four mucosa associated lymphoid tissue (MALT) lymphomas were identified; the primary sites included lung (two occurrences), stomach (one occurrence), and salivary gland (one occurrence).

Table 1. Characteristics of Children With HIV-Associated Malignancies

Characteristic	No. of Children	%
Sex		
Male	39	61
Female	25	39
Race/ethnicity		
White	32	50
Black	19	30
Hispanic	12	19
Filipino	1	2
Mode of HIV transmission		
Vertical	37	58
Blood transfusion	22	34
Sexual	3	5
Organ transplant	1	2
Unknown	1	2
Mode of transmission		
	Vertical	Transfusion
Age at cancer diagnosis, years		
Median	4.3	13.4
Range	1.1-9.8	0.7-21
Latency,* years		
Median	4.3	10.4
Range	1.1-9.8	0.6-13.8

NOTE. Total no. of children = 64.

*Time from HIV infection to cancer diagnosis imputed based on estimated dates (see text).

Smooth Muscle Tumors

Only three of our 11 cases of smooth muscle tumors had their primary location in the GI tract, which normally accounts for the majority of cases in nonimmunosuppressed children (Table 3).¹⁶

Relative Risk of Specific Cancers in HIV-Infected Children

For the 1,328 person-years of observation at the NCI, 0.013 cases of childhood NHL would have been expected compared with the 16 NHL cases observed; thus the SIR was 1,203 (95% confidence interval [CI], 688 to 1,949). For leiomyosarcomas, 0.0002 cases were expected compared with the two cases observed for an SIR of 10,000 (95% CI, 1,210 to 36,100).

Treatment

Forty-eight children (75%) were treated, nine children (14%) received palliative care or no treatment, and seven cancers (11%) were diagnosed incidentally at the time of autopsy. Of those with NHL who received treatment (35 of 42 children; 83%), seven of 20 children from CCG institutions were treated according to cooperative group protocols; 12 of 15 children from the NCI were treated according to NCI protocols. Multiagent chemotherapy for all NHLs consisted of two or more of the following drugs: cyclophosphamide, vincristine, methotrexate, prednisone, doxorubicin, and cytarabine. Treatment for smooth muscle tumors

consisted of surgical excision, chemotherapy, radiation therapy, and/or interferon- α .

Response to Treatment

A complete response was defined as the absence of clinically detectable malignant disease and normal radiographic studies at any previously abnormal sites for at least 4 weeks. A partial response was defined as a decrease of at least 50% of the tumor burden that lasted at least 4 weeks. Stable disease was defined as a less than 50% reduction of the tumor burden.

For all treated cancers combined, there were 30 (63%) complete responders, 12 (25%) partial responders, four (8%) with stable disease, and two (4%) children did not complete therapy. For all children with NHL who were treated, there were 19 (54%) complete responders, 11 (31%) partial responders, three (9%) with stable disease, and two (6%) who did not complete therapy.

Survival Studies

Seven cases diagnosed at autopsy were not included in the analysis of survival. The median survival time of children diagnosed with smooth muscle tumors was 12 months (range, 10 days to 19 months) and of children with NHL was 6 months (range, 1 day to 89 months; Figs 1A, C, and E). We examined the CCG and the NCI NHL survival data separately because the children were selected differently and

Table 2. Pathologic, Clinical, and Immunologic Features of NHLs in HIV-Infected Children

Characteristic	CCG (n = 26)		NCI (n = 16)	
	No.	%	No.	%
Histology				
Immunoblastic/LCL	11	42	7	44
SNCL	11	42	4	25
MALT	1	4	3	19
Plasmacytoid	1	4	1	6
Unknown subtypes	2	8	1	6
Extranodal disease				
Yes	22	85	13	81
No	4	15	3	19
Phenotype				
B cell	15	88	10	62
T cell	2	8	2	13
Non B, non T	1	4	1	6
Unknown	8	31	3	19
Immune status at diagnosis of NHL				
CD4 percentage				
No evidence of suppression, ≥ 25	5	19	2	13
Evidence of moderate suppression, 15-24	3	12	1	6
Severe suppression, < 15	11	42	13	81
Unknown	7	27	0	0

NOTE. Percentages do not always add to 100 because of rounding.

Abbreviations: LCL, large-cell lymphoma; SNCL, small noncleaved cell lymphoma.

Table 3. Clinical Data on Children With Smooth Muscle Tumors

Age at Tumor Diagnosis (years)/Sex	Race or Ethnic Group	Mode of HIV Transmission	CD4% at Tumor Diagnosis	Location	Survival
9/F	Black	Vertical	0	Liver	13 months*
7/F	White	Vertical	2	Ileum, colon	Autopsy*
3/M	Black	Vertical	1	Liver	Autopsy*
12/M	White	Neonatal transfusion	0	Spleen	Autopsy
6/F	Hispanic	Vertical	2	Lung	2 months†
8/F	White	Vertical	15	Liver	10 days
18/M	White	Factor VIII transfusions	0	Forearm	9 months
6/M	Black	Vertical	7	Colon with lung metastases	5 months
9/F	Black	Vertical	NA	Sacrum	12 months
4/F	White	Vertical	16	Colon	14 months
9/M	Filipino	RBC transfusions	3	Spleen	19 months

NOTE. Because histologic features of smooth muscle tumors are not necessarily predictive of biologic behavior, benign (leiomyoma) and malignant (leiomyosarcoma) tumors are considered together.³⁷

Abbreviation: NA, not available.

*Previously reported.¹³

†Alive at last follow-up.

treated according to different protocols. Survival after NHL was substantially longer in the NCI cohort compared with the CCG cohort. Of note, of those assessable for survival, five of 25 (20%) CCG children with NHL and one of 14 (7%) NCI children with NHL were not treated for cancer.

The average monthly death rate for all children with NHL was 12% per month in the first 6 months after diagnosis; then the monthly death rate decreased and stabilized to approximately 2% per month. For children with NHL from the CCG, the monthly death rate was very high at 35% per month 1 month after diagnosis; then it decreased by 86% to 5% per month 6 months after NHL diagnosis (Fig 1D). The monthly death rate for children with NHL from the NCI was relatively low; 3% per month 6 months after diagnosis (Fig 1F). In contrast, the monthly death rate for children with

smooth muscle tumors from the CCG increased from 8% per month 1 month after diagnosis to 20% per month 12 months after diagnosis (Fig 1B). Children with smooth muscle tumors from the NCI were not evaluated because three of five cases were discovered at autopsy.

Prognostic Factors

For children with NHLs in the CCG cohort, younger age (as a continuous variable), vertical transmission, and lowest (≤ 7) CD4 percentage tertile were significantly associated with shortened survival in univariate analysis. In multivariable models that considered the factors found to be significant in the univariate analyses, younger age and low CD4 percentage remained as significant and independent predictors of shorter survival (Table 4).

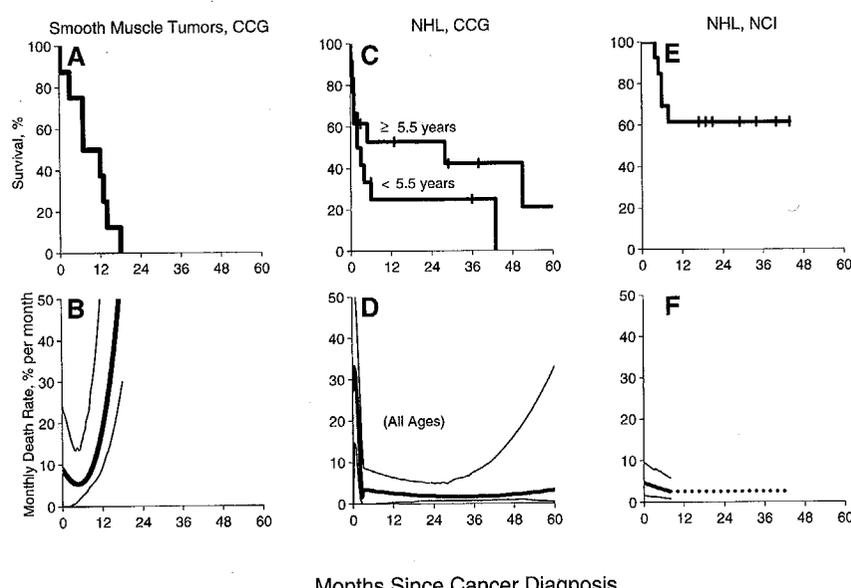


Fig 1. Survival of HIV-infected children with cancer and corresponding monthly death rates; (A, B) smooth muscle tumors from the CCG, (C, D) NHLs from the CCG, (E, F) NHLs from the NCI. In (B, D, F) (thicker solid curves) show the point estimates; (thinner solid curves) show pointwise 95% confidence limits. (F) The NCI hazard is extrapolated. Ticks represent censored subjects.

Table 4. Multivariable Analysis of Risk Factors for NHLs in the CCG Patients

Risk Factor	Relative Hazard	95% CI
Age, per 5-year decrease	2.1	1.1-4.1
Tertiles of CD4 percentage		
≤ 7 v ≥ 17	6.5	1.1-36.5
8-16 v ≥ 17	1.3	0.2-7.6

DISCUSSION

This is the largest case series assembled to date of HIV-associated malignancies in children. Our study confirms a predominance of NHLs and smooth muscle tumors reported in smaller case series.^{13,17-20} The relative risk for a child with HIV infection to develop NHL was calculated to be 1,200 times greater than expected in healthy children of the same age. For leiomyosarcomas, normally exceedingly rare in children, the relative risk was 10,000. Notably, leiomyosarcoma cases are not detected by AIDS surveillance. Because cases were identified retrospectively, these calculations may be an underestimate. However, because of the profound nature of HIV infection and cancer, it is unlikely that either a principal investigator or other staff members would not recall cases.

Similar to the presentation of NHL in the general pediatric population, HIV-infected children presented with high-grade, predominantly B-cell lymphomas in extranodal sites. Sixty percent to 90% of NHLs in adults with HIV infection were also extranodal, and the vast majority had aggressive histologies.²¹ The GI tract and CNS are common extranodal sites for both adults and children. Forty-three percent of NHLs in our series were of large-cell histology (immunoblastic, diffuse, or anaplastic), whereas only about 20% of NHLs in nonimmunosuppressed children are large-cell lymphomas.²² Of interest, Rabkin and Yellin²³ reported an increasing number of large-cell immunoblastic and diffuse large-cell histologies compared with small noncleaved cell histologies (which peaked and remained stable) in a study of HIV-related cancers in adults.²³ All primary CNS lymphomas in our series were of large-cell type, consistent with findings reported in adults. Thus, both adults and children share a distinguishing feature of HIV-related NHL: aggressive, widespread disease at presentation.

MALT lymphomas normally occur in the sixth or seventh decade of life and are characterized by indolent behavior, good response to treatment, and favorable long term survival.²⁴ Several cases in patients younger than 19 years of age have previously been described in the literature.^{14,15,25-27} Whereas these lymphomas are rarely found in HIV-infected adults,²⁸ MALT lymphomas comprised 10% of all NHLs in this pediatric series. It has been suggested that pulmonary lymphoid hyperplasia/lymphoid interstitial pneumonitis complex represents a benign, reactive MALT lesion²⁵ and is an

indicator of AIDS in children. Perhaps MALT lymphomas should be considered AIDS-defining in children as well.

In adults, total lymphoma incidence is associated with increasing duration of HIV infection and progression in immune dysregulation. The Multicenter AIDS Cohort Study (MACS) analyzed the incidence of NHL in 2,627 HIV-infected homosexual men in the United States and noted a nonsignificant increase in NHL incidence with decreasing CD4+ T-cell count; the relative risk of NHL as an initial AIDS-defining diagnosis was 0.38 (95% CI, 0.14 to 1.09) with 101 to 200 CD4+ cells/μL versus 100 cells/μL,²⁹ or less. In almost one third of the children in our study, NHL occurred with moderate or no evidence of severe immunosuppression. Thus, as in adults, severe immunosuppression as measured by depletion of CD4+ T lymphocytes did not appear to be a prerequisite for the development of NHL in children. Functional abnormalities of T cells that are not reflected by CD4+ lymphocyte numbers may contribute to tumor development.³⁰

Natural history studies of systemic AIDS NHL in adults have shown a median survival of approximately 4 to 6 months.^{31,32} The prognosis tends to be poor because of the aggressive behavior of the malignancy and the underlying immunosuppression of the individual. In our study, children younger than 5 years of age with NHL fared worse than older children. This was not surprising, because vertically infected infants develop immunodeficiency and related illnesses faster than adults.² The immature level of the immune system at the time of HIV acquisition may partially explain this difference.³⁰

Although we did not strictly formulate an a priori hypothesis concerning survival, we found that the survival experience after NHL diagnosis was more favorable at the NCI than at CCG institutions. We must also emphasize that the small number of cases assessable for survival (CCG, 20 cases; NCI, 13 cases) limits the validity of conclusions regarding survival. Children from both cohorts had similar characteristics that may affect survival, such as the mode of HIV transmission, prior AIDS diagnosis, presence of extranodal disease, and median CD4 percentage, although the median age at the time of NHL diagnosis in the CCG cohort was 5 years compared with 8 years in the NCI cohort.

The favorable experience at the NCI may reflect selection bias. Children must satisfy a specific set of criteria to be eligible for NCI protocols and thus may be better able to cope with cancer than children treated at CCG hospitals. In addition, children at the NCI were under close observation for progression of HIV disease (the majority were enrolled in antiretroviral protocols) and perhaps NHL may have been diagnosed earlier than in children followed in the general pediatric community. Without close follow-up, NHL diagnosis can be delayed in the setting of HIV disease because

many symptoms of lymphoma can be confused with HIV manifestations. For example, fever, abdominal pain, and night sweats can be because of opportunistic infections with *Mycobacterium avium-intracellulare* or cytomegalovirus. Furthermore, many children with HIV infection develop lymphadenopathy. CNS lymphoma can present with neurologic symptoms and head computerized tomography abnormalities that are identical to toxoplasmosis. Because pediatric NHL can be highly aggressive, early diagnosis and expeditious management are essential for a successful outcome.

Whereas selection bias or earlier diagnosis may partly explain the longer survival of children with NHL at the NCI, it is also possible that treatment modalities may have contributed to this observation. Cases followed up at the NCI were enrolled in HIV-related cancer protocols, whereas less than half of the CCG cases were treated according to cooperative group protocols. HIV-related cancer therapeutic protocols may have been superior, or there may simply be a benefit from the standardized treatment approach prescribed by a protocol. Randomized clinical trials that compared standard pediatric NHL protocols to HIV-related NHL protocols would be essential to determine any differences in intervention.

In contrast to the relatively stable mortality rate for children with NHL, mortality rates for children with smooth muscle tumors increased over time. For nonimmunosup-

pressed children, wide local excision is the most common treatment modality and prognosis is good for tumors outside the GI tract but poor for tumors that arise within the GI tract.³³ Experience with other treatment modalities (chemotherapy, radiation, immunomodulatory therapy) is limited, and optimal therapy in children with HIV infection is yet to be defined.

As children with HIV survive longer because of better antiretroviral and supportive therapies, HIV-related malignancies may become an increasingly common concern. Despite the dual burden of HIV and cancer, many of these children often respond well to therapy. Although some children may not be candidates for intensive treatment, lower intensity anticancer regimens that include aggressive supportive care and concomitant antiretroviral therapy may yield high survival rates.^{34,35} Although NHL and leiomyosarcoma are the most common malignancies in HIV-infected children, their pathogenesis is not completely understood. Of interest are recent reports of an association between Epstein-Barr virus and leiomyosarcomas in immunosuppressed children and young adults.^{36,37} Multicenter clinical trials are needed to show which treatments are most effective and to facilitate biologic studies of HIV-associated malignancies in children.

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