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Short-Term Risk of HIV-Disease Progression and Death in Ugandan Children Not Eligible for Antiretroviral Therapy

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Abstract

Background—Increasing numbers of HIV-infected children not yet eligible for antiretroviral therapy (ART) are entering health care in Africa. We sought to characterize the risk of short-term disease progression in this population.

Methods—In a cohort of HIV-infected ART-naive and -ineligible Ugandan children >1 year old, the rates of clinical/immunologic progression within 2 years were assessed using Kaplan–Meier survival analysis and multivariate Cox proportional-hazards modeling.

Results—Among 192 children (mean age: 6.4 years, CD4%:25), 19% progressed within 2 years by WHO-stage 3/4 event(n=22), death (n=3), or WHO-defined CD4 threshold for ART-initiation(n=12). Significant univariate predictors were CD4%(HR=2.0 per 10% decrease, p=0.005), HIV-RNA level(HR=2.4 per log10 increase, p=0.002), male gender (HR:2.0, p=0.04), age < 3 years (HR=3.7, p=0.001), CD4-activation [%CD4+CD38+HLADR+] (HR=1.6 per 10% increase, p=0.05) and CD8-activation [%CD8+CD38+HLADR+](HR=1.3 per 10% increase, p=0.05] (HR=1.3, p=0.5). In multivariate analysis, CD4%(HR=2.0, p=0.034), HIV-RNA level(HR=1.8, p=0.013) and age < 3 years (HR:3.0, p=0.008) were independently predictive. Children with HIV-RNA >10^5 copies/ml and CD4% <25 had progression rates of 29% (1 year) and 34% (2 years).

Conclusions—Even with frequent CD4 monitoring, HIV-infected Ugandan children experienced significant clinical events while ineligible for ART. Alternate strategies for monitoring or ART-initiation may be needed to improve outcomes.

Keywords

HIV; children; progression; monitoring; resource-limited

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INTRODUCTION

There are currently 2 million children living with HIV, 90% of whom live in Africa [1]. Current World Health Organization guidelines recommend antiretroviral therapy (ART) for all HIV-infected children less than one year of age [2]. For older children, ART is only recommended in the context of CD4 cell suppression or clinical HIV-disease progression [3]. With the expansion of community and home based testing programs in Africa, a growing number of HIV-infected children who survived infancy and may not yet meet criteria to start ART are being recognized [4]. There are limited data about predictors of clinical progression in this population and none which include HIV RNA levels.

The purpose of this analysis was to evaluate the risk and predictors of short-term immunologic and clinical HIV progression among a cohort of Ugandan children not meeting criteria for antiretroviral therapy. Insight into HIV-disease progression in this growing population has implications for optimal clinical monitoring strategies and will add to the current debate about the optimal time to initiate antiretroviral therapy in HIV-infected children in Africa and other resource-limited settings [5].

METHODS

Study participants

This study included ART-naive HIV-infected Ugandan children selected from an existing cohort, the Children with HIV and Malaria Project (CHAMP) [6]. From October 2005 to August 2006, CHAMP enrolled 300 HIV-infected children from a pediatric HIV clinic in Kampala, Uganda using convenience sampling. Inclusion criteria for CHAMP were: (1) documented HIV-1 infection; (2) age 1 to 10 years; (3) living within a 20 km radius of the clinic; (4) weight > 5 kg; (5) agreement to come to the study clinic for any febrile episode or other illness; (6) agreement to remain in Kampala for the duration of the study; (7) agreement to avoid medications administered outside the study protocol; and (8) willingness of parents or guardians to provide informed consent. Children had HIV-infection documented by ELISA test kit and confirmed by Western blot or PCR viral load assay prior to study entry. Any child meeting Ugandan criteria on enrollment was started on ART. During the study period, Ugandan guidelines matched the 2006 World Health Organization guidelines [7] and included age specific CD4 count and percentage thresholds, WHO stage III diagnoses (excluding pulmonary tuberculosis, lymphoid interstitial pneumonitis, oral hairy leukoplakia, and thrombocytopenia), and any WHO Stage IV diagnosis. All CHAMP children that were ART-naïve and ineligible for ART initiation upon enrollment were included in this study.

Study participant follow-up

Children were followed in a study clinic that was open every day. New medical problems underwent standardized medical evaluation and coding that was based on WHO clinical staging criteria. All WHO stage 3 and 4 endpoints were independently reviewed by an HIV clinician. Study participants were withdrawn if they moved out of the study area, could not be located for any consecutive 60-day period, withdrew consent, or died. All participants were prescribed daily trimethoprim-sulfamethoxazole (TS) and provided with insecticide treated bed-nets for the prevention of malaria.

Laboratory methods

Complete blood cell counts (AcT5diff; Beckman Coulter, Brea, CA), plasma HIV RNA level (level of detection of 400 copies/mL, Roche Amplicor Version 1.5, Pleasanton, CA), and CD4 cell count and percentage (FACS Calibur, Becton Dickinson, San Jose, CA) were

measured every 12 weeks at a College of American Pathologists-certified laboratory in Kampala, Uganda. Levels of T-cell activation, defined as % of CD4 and CD8 cells expressing both CD38 and HLADR were determined at one time for each child within a median of 84 days from enrollment (IQR:0-168) using freshly isolated peripheral blood mononuclear cells, as described elsewhere [8].

Statistical analysis

The combined primary endpoint of disease progression was defined as development of a WHO stage 3 or 4 clinical event, death or CD4 measure decline below 2006 WHO-defined age-specific thresholds for ART initiation [12-35 months: CD4 % < 20 or count < 750 cells/mm^3; 36-59 months: CD4 % < 15 or count < 350 cells/mm^3, ≥ 60 months: < 350 cells/mm^3) [3]. Time to disease progression was evaluated by Kaplan- Meier survival analysis, multivariate Cox proportional hazards modeling or non-parametric techniques, depending on the data. Variables significantly associated with progression in univariate analysis at the p=0.1 level were chosen for inclusion for evaluation in multivariate modeling. Only those variable which retained significance ($p<0.05$) in the multivariate model were included in the final model. Potential independent predictor variables were evaluated for colinearity by examining non-parametric rank correlation coefficients and a variety of models were tested and compared using −2 log likelihood measures for goodness of fit. For children who were lost to follow up, data were censored as of the last visit date and they were not considered to have progressed. Data were double-entered in Access (Microsoft, Bellevue, WA), and statistical analysis was performed using SPSS (SPSS Worldwide Headquarters SPSS Inc., Chicago, IL).

Ethical approval

Approval for this study was obtained from the Uganda National Council of Science and Technology, the Makerere University Research and Ethics Committee, and the University of California, San Francisco Committee on Human Research. The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000.

RESULTS

Study participants and baseline characteristics

A total of 192 ART-naïve children were not eligible to start ART by Ugandan / WHO guidelines and included in this study. The median age for study participants was 6.4 years (range 1-11); 83 subjects (43%) were male. Mean baseline CD4% was 24 (range 8-46) and mean $\log_{10}$ HIV RNA copies/ml was 5.0 (range undetectable to > 6.0 Log_{10} copies/ml) (Table 1).

HIV Disease Progression Events

A total of 37 (19%) children progressed to a WHO stage 3 or 4 clinical event, died or reached the age-specific CD4 threshold for ART initiation after a median 605 days (IQR: 280-700) days follow up per child. 7 children were lost to follow up during the study period. At baseline, progressors included significantly more children 1-3 years of age and had lower mean CD4 cell count percentage and hemoglobin levels, but higher HIV RNA, CD4 and CD8 activation levels compared to nonprogressors (Table 1). Among the 37 children who were observed to have short-term HIV disease progression, 25 (43%) progressed clinically, with either a new WHO stage 3 or 4 diagnosis or death (Table 2). The most frequent clinical progression event was recurrent bacterial pneumonia (n=6), followed by pulmonary tuberculosis (n=5), death (n=3) and symptomatic lymphyocytic interstitial pneumonia (n=3).

Oral candidiasis, moderate malnutrition, extra-pulmonary TB, intermittent fevers, chronic lung disease, persistent fevers, and thrombocytopenia were each seen in 1 or 2 children.

Predictors of progression

CD4% [HR: 2.0 p=0.005 for each 10% lower), $\log_{10}$ HIV RNA (HR: 2.4 per unit log increase, p=0.002), male gender (HR: 2.0, p=0.04), age less than 3 years (HR=3.7, p=0.001), CD4 activation level (HR: 1.6 per 10% increase, p=0.05), CD8 activation level (HR: 1.3 per 10% increase, p=0.05) were significant univariate predictors by Cox proportional hazards modeling (Table 3). Age, Z-score weight-for-age, hemoglobin < 9 g/dl, and absolute CD4 cell count were not associated with progression. In multivariate analysis, CD4% (HR=2.0 per 10% decrease, p=0.013), HIV RNA level (RH=1.8, p=0.034) and age < 3 years (HR:3.0, p=0.008) were predictive. In Kaplan–Meier analysis of progression free survival among the 192 children, baseline HIV RNA >100,000 copies/ml [p=0.03] was predictive of progression, as was a combination of RNA>100,000 and CD4% < 25 at baseline [p=0.01], however CD4% < 25 alone as a dichotomy was not [p=0.15] (Figure 1). Among children with levels of HIV RNA<100,000 copies/ml and CD4% > 25%, 11% and 15% progressed within 1 and 2 years, respectively (Table 4). In contrast, among children with levels of HIV RNA>100,000 copies/ml and CD4% < 25%, 29% and 34% progressed within 1and 2 years, respectively.

DISCUSSION

The WHO recently reported that the mean age of starting ART in HIV-infected African children is 5-9 years [9]. As testing programs expand throughout Africa, increasing numbers of HIV-infected children in this age range will be identified [4]. It is critical that the risk of and factors contributing to disease progression for this growing population be understood.

In this study of 192 HIV-infected children with a median age of 6.4 years, we found that 19% progressed with clinical events or immunologic decline within 2 years. CD4%, HIV RNA level, and age less than 3 years were independently predictive of HIV-disease progression. These findings are similar to those from studies of children in the USA and Europe, which have shown CD4% and HIV RNA level to be important predictors of short term disease progression [10, 11] and mortality [11, 12]. There have been only a few studies examining predictors of HIV-disease progression in children living in resource-limited settings, and they have primarily focused on infants[13, 14] or children under 3 years of age [15]. The largest study of older HIV-infected children, a recently published meta-analysis of 9 African and 1 Brazilian cohorts, found that CD4 count and weight-for age were the strongest predictors of mortality; however this study did not have adequate data to evaluate HIV RNA level, and adjustments were made for variable usage of trimethoprim-sulfmethoxazole, a strong factor in mortality[16]. Notably, most of these studies included children with advanced disease and low CD4 counts that would be eligible for ART based on current guidelines. In our study of children not eligible for ART, HIV RNA level and a decrease in CD4%, were important predictors of short term disease progression in HIV-infected African children.

We also found that CD4 and CD8 cell activation levels were significant univariate predictors of HIV disease progression. Several prospective studies of adults in the USA and Europe showed that levels of CD8[17-19] and CD4[20] cell activation predicted disease progression, with similar results for children [21, 22]. We previously showed that HIV-infected Ugandan children in our cohort had higher levels of T-cell activation compared to HIV-uninfected Ugandan controls[23], and that reduction of T-cell activation seemed important to CD4 recovery with ART [8], as has been shown for adults[24] and children[25] in the USA and Europe. The present study builds on these findings, showing elevated levels of CD4 and CD8 activation to be significant univariate predictors of disease progression specifically among

HIV-infected children with CD4 counts and percentages above the threshold for ART initiation. After adjustment for CD4 percent and HIV viral load, the hazard ratio for measures of immune activation changed little (data not shown), suggesting an independent effect, but lost statistical significance due to the number of predictors in the model and the small number of observed progression events. It will be important to elucidate the impact of immune activation on HIV-disease in African children because data suggest that Africans have higher levels of T-cell activation compared to European controls, presumably related to non-HIV infectious burden [26, 27].

Among the HIV-infected children who progressed during the follow up period, 43% did so by experiencing a new WHO stage 3 or 4 clinical event, or death. These events occurred in our cohort which benefited from a level of monitoring beyond what is possible in most limited resource settings. Improved preventive care such as pneumococcal vaccination or isoniazid preventive therapy would likely decrease some HIV-related morbidity. It is also plausible that ART initiation in African children at higher CD4 levels could additionally reduce this HIV-related morbidity, but this strategy requires further evaluation.

The optimal timing for the initiation of ART in HIV-infected children continues to be a topic of much debate and ongoing study. With few data from resource-limited settings, the 2006 WHO treatment guidelines for children were based on progression data primarily from HIV-infected children in the USA and Europe [11, 28, 29]. But recent studies have shown that children in resource-limited settings suffer higher mortality at any given CD4 value compared to children in resource rich countries[16]. In 2008, the WHO modified guidelines for ART initiation in children 36-95 months of age, raising the CD4% cutoff to 20% [2]; on re-examination of our data, this change would have led to earlier initiation of ART in a few children, but not among those that experienced clinical events. In 2009, the WHO similarly raised the CD4 count thresholds for treatment of adolescents[30]. For infants less than 12 months of age, the WHO now recommends universal ART regardless of immune status,[2] because of studies in South Africa that demonstrated early initiation of ART significantly decreases mortality this age group,[31] Our findings here, that children older than 12 months continue to suffer significant morbidity while ineligible for ART, underscore the need for controlled clinical studies investigating the potential benefits of ART initiation at higher CD4 thresholds in this age group.

Limitations of our study include its small size, which reduced the power to evaluate all baseline variables. Children enrolled in this study constituted a healthy survivor cohort, comprised of children that escaped the very high infant mortality associated with HIV infection. The exclusion of children with low weight (<5 kg) and residence greater than 20 kilometer from our clinic and the loss of 7 children to follow up may have led to underestimates of disease progression. Our analysis was also limited by the fact that children with high HIV RNA levels had generally low CD4 percentages; such colinearity in variables makes it difficult to establish truly independent effects in multivariate models.

In summary, in this cohort of HIV-infected Ugandan children over 1 year of age, nearly one fifth experienced disease progression within 2 years of enrollment, with half experiencing WHO stage III clinical disease. CD4 % was the strongest laboratory predictor of HIV disease progression and death, followed by HIV RNA levels. The high rate of HIV related clinical disease in this cohort prior to meeting ART initiation criteria underscores the importance of close monitoring and research on optimal timing of ART in children.

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References

1. UNAIDS. Report on the Global AIDS Epidemic - Executive Summary. [accessed on July 28, 2009]. 2008 www.data.unaids.org/pub/GlobalReport/2008/JC1511_GR08_ExecutiveSummary_en.pdf
2. WHO. Paper presented at: Paediatric HIV/ART Care Guideline Group Meeting; WHO Headquarters, Geneva, Switzerland. April 10-11, 2008; Report of the WHO Technical Reference Group
3. Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access. World Health Organization; Geneva: 2006.
4. Were WA, Mermin JH, Wamai N, et al. Undiagnosed HIV infection and couple HIV discordance among household members of HIV-infected people receiving antiretroviral therapy in Uganda. J Acquir Immune Defic Syndr Sep;2006 43(1):91–95. [PubMed: 16885775]
5. Abrams EJ. The unanswered question: when to initiate antiretroviral therapy in children with HIV infection. Curr Opin HIV AIDS 2007;2:416–425. [PubMed: 19372921]
6. Kamya MR, Gasasira AF, Achan J, et al. Effects of trimethoprim-sulfamethoxazole and insecticide-treated bednets on malaria among HIV-infected Ugandan children. Aids Oct 1;2007 21(15):2059–2066. [PubMed: 17885296]
7. _on_Pediatric_HIV_Care_and_Treatment TRG. Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access. World Health Organization; [accessed July 28, 2009]. 2006 p. 158www.who.int/hiv/pub/guidelines/paediatric020907.pdf
8. Ruel T, Ssewanyana I, Achan J, et al. Dynamics of T cell activation accompanying CD4 recovery in antiretroviral treated HIV-infected Ugandan children. Clin Immunol. Mar 18;2009
9. Children and AIDS: Second stocktaking report. UNAIDS; Geneva: 2008.
10. Palumbo PE, Raskino C, Fiscus S, et al. Predictive value of quantitative plasma HIV RNA and CD4+ lymphocyte count in HIV-infected infants and children. Jama Mar 11;1998 279(10):756–761. [PubMed: 9508151]
11. HIV Paediatric Prognostic Markers Collaborative Study G. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. The Lancet 2003;362(9396):1605–1611.
12. Mofenson LM, Korelitz J, Meyer WA 3rd, et al. National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. The relationship between serum human immunodeficiency virus type 1 (HIV-1) RNA level, CD4 lymphocyte percent, and long-term mortality risk in HIV-1-infected children. J Infect Dis May;1997 175(5):1029–1038. [PubMed: 9129063]
13. Taha TE, Graham SM, Kumwenda NI, et al. Morbidity Among Human Immunodeficiency Virus-1-Infected and -Uninfected African Children. Pediatrics December 1;2000 106(6):e77. 2000. [PubMed: 11099620]
14. Rouet F, Sakarovitch C, Msellati P, et al. Pediatric viral human immunodeficiency virus type 1 RNA levels, timing of infection, and disease progression in African HIV-1-infected children. Pediatrics Oct;2003 112(4):e289. [PubMed: 14523214]
15. Taha TE, Kumwenda NI, Hoover DR, et al. Association of HIV-1 load and CD4 lymphocyte count with mortality among untreated African children over one year of age. Aids Mar 10;2000 14(4): 453–459. [PubMed: 10770550]
16. Markers for predicting mortality in untreated HIV-infected children in resource-limited settings: a meta-analysis. Aids Jan 2;2008 22(1):97–105. [PubMed: 18090397]
17. Giorgi JV, Liu Z, Hultin LE, Cumberland WG, Hennessey K, Detels R, The Los Angeles Center, Multicenter AIDS Cohort Study. Elevated levels of CD38+ CD8+ T cells in HIV infection add to the prognostic value of low CD4+ T cell levels: results of 6 years of follow-up. J Acquir Immune Defic Syndr Aug;1993 6(8):904–912. [PubMed: 7686224]

18. Liu Z, Hultin LE, Cumberland WG, et al. Elevated relative fluorescence intensity of CD38 antigen expression on CD8+ T cells is a marker of poor prognosis in HIV infection: results of 6 years of follow-up. Cytometry Mar 15;1996 26(1):1–7. [PubMed: 8809474]
19. Mocroft A, Bofill M, Lipman M, et al. CD8+,CD38+ lymphocyte percent: a useful immunological marker for monitoring HIV-1-infected patients. J Acquir Immune Defic Syndr Hum Retrovirol Feb 1;1997 14(2):158–162. [PubMed: 9052725]
20. Hazenberg MD, Otto SA, van Benthem BH, et al. Persistent immune activation in HIV-1 infection is associated with progression to AIDS. Aids Sep 5;2003 17(13):1881–1888. [PubMed: 12960820]
21. Paul ME, Shearer WT, Kozinetz CA, Lewis DE. Comparison of CD8+ T-cell subsets in HIV-infected rapid progressor children versus non-rapid progressor children. Journal of Allergy and Clinical Immunology 2001;108(2):258–264. [PubMed: 11496243]
22. Resino S, Correa R, Bellon JM, Munoz-Fernandez MA. Preserved immune system in long-term asymptomatic vertically HIV-1 infected children. Clinical and Experimental Immunology 2003;132(1):105–112. [PubMed: 12653844]
23. Ssewanyana I, Elrefaei M, Dorsey G, et al. Profile of T Cell Immune Responses in HIV-Infected Children from Uganda. J Infect Dis Dec 1;2007 196(11):1667–1670. [PubMed: 18008251]
24. Hunt PW, Martin JN, Sinclair E, et al. T cell activation is associated with lower CD4+ T cell gains in human immunodeficiency virus-infected patients with sustained viral suppression during antiretroviral therapy. J Infect Dis May 15;2003 187(10):1534–1543. [PubMed: 12721933]
25. Resino SSE, Gutierrez MD, Leon JA, Munoz Fernandez MA. CD4+ T-Cell Immunodeficiency Is More Dependent on Immune Activation Than Viral Load in HIV-Infected Children on Highly Active Antiretroviral Therapy. Journal of acquired immune deficiency syndromes 2006;42(3): 269–276. [PubMed: 16810122]
26. Rizzardini G, Trabattoni D, Saresella M, et al. Immune activation in HIV-infected African individuals. Italian-Ugandan AIDS cooperation program. Aids Dec 24;1998 12(18):2387–2396. [PubMed: 9875576]
27. Vigano, ASM.; Natascia, S.; Fossati, S.; Bricalli, D.; El Abbar, M.; Al Tawaty, A.; Principi, N.; Clerici, M. Immune activation in a cohort of horizontally HIV-infected Lybian children; Int Conf AIDS 2000; July 9-14, 2000; 2000. p. 13abstract no. MoPeB2191
28. Treatment WTRGoPHCa. Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access. 2006. p. 158www.who.int/hiv/pub/guidelines/paediatric020907.pdf
29. Dunn D. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. Lancet Nov 15;2003 362(9396):1605–1611. [PubMed: 14630440]
30. Rapid Advice: antiretroviral therapy for adults and adolescents. World Health Organization; Nov. 2009
31. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. N Engl J Med Nov 20;2008 359(21):2233–2244. [PubMed: 19020325]

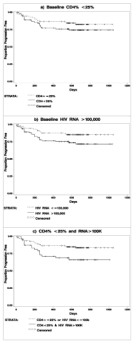

Figure 1. Progression Free Survival by Baseline CD4 and HIV Viral Load

Kaplan-Meier survival analysis by baseline CD4% less than 25% (a), HIV RNA greater than 100,000 copies/ml(b), and both (c).

Table 1

Baseline Subject Characteristics

		All	Progressors	Non-Progressors	p-value*
Number of Subjects		192	37	155	
Age – Mean years (SD)		6.4 (2.3)	5.9 (2.7)	6.6 (2.2)	0.23
Age - N (% of total)	1-3 years	16 (8)	8 (22)	8 (5)	0.003
	>3-5 years	30 (16)	2 (5)	28 (18)	
	>5 years	146 (76)	27 (73)	119 (77)	
Sex - N (% of total)	Male	83 (43)	21 (57)	62 (40)	0.07
	Female	109 (57)	16 (43)	93 (60)	
CD4 Count – Mean cells/μl (SD)		839 (449)	825 (440)	842 (452)	0.92
CD4% - Mean (SD)		25 (8.0)	23 (7.2)	26 (8.0)	0.04
CD4 Cell % - N (% of total)	≤ 25%	105 (55)	24 (65)	81 (52)	0.20
	> 25%	87 (45)	13 (35)	74 (48)	
HIV RNA – Mean Log_{10}(c/ml) (SD)		4.8 (0.8)	5.2 (0.5)	4.8 (0.8)	0.002
HIV RNA - N (% of total)	< 400 c/ml	5 (3)	0 (0)	5 (3)	0.21
	400-10,000 c/ml	12 (6)	0 (0)	12 (8)	
	>10,000 – 100,000 c/ml	77 (40)	13 (35)	64 (41)	
	>100,000 – 750,000 c/ml	80 (42)	20 (54)	60 (39)	
	>750,000 c/ml	18 (9)	4 (11)	14 (9)	
Hemoglobin - Mean g/dl (SD)		11.6 (1.3)	11.3 (1.6)	11.7 (1.2)	0.05
Hemoglobin < 9g/dl - N (% of total)		7 (4)	3 (8)	4 (3)	0.13
Z-Score Weight for Age – Mean (SD)		−1.5 (1.3)	−1.6 (1.7)	−1.4 (1.1)	0.59
% CD4 Activation^ – Mean (SD)		13 (6.5)	16 (5.9)	13 (6.6)	0.023
% CD8 Activation^ – Mean (SD)		43 (13.6)	48 (13)	42 (14)	0.053

*P-value for the comparison between progressors and non-progressors using Fisher Exact or Wilcoxon Two-Sample Test as indicated.

^% of cells expressing both CD38+HLADR+, available from 139 children, 30 of whom progressed. C/ml = copies/milliliter.

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Table 2

Clinical Progression Events

Enrollment				*Event*		
Age (years)	**WHO Stage**	**CD4 cells/µl (%)**	**HIV RNA copies/ml**	**WHO Stage 3 or 4 Event**	**Event Day***	**Recent CD4 cells/µl (%)†**
5	2	673 (15)#	21,053	Death (meningitis)	87	n/a
7	2	319 (15) #	286,069	Death (pneumonia)	231	681 (18)
5	3	752 (23)	290,476	Death (stroke)[a]	55	n/a
10	2	1206 (26)	80,712	Extra-Pulmonary TB	541	752 (18)
3	3	1044 (25)	434176	Malnutrition	644	960 (26)
9	2	507 (8) #	528,371	Malnutrition	280	500 (6)
6	1	1112 (42)	63,681	Oral candidiasis	80	n/a
7	2	443 (12) #	403,195	Persistent fevers	68	n/a
7	1	244 (29)	61,000	Persistent fevers	182	249 (18)
5	2	939 (25)	250,387	Pulmonary TB	7	n/a
1	1	1883 (28)	366,095	Pulmonary TB	4	n/a
5	1	1779 (28)	>750,000	Pulmonary TB	198	968 (28)
7	1	882 (22)	83,710	Pulmonary TB	264	750 (20)
5	2	1399 (36)	229,562	Pulmonary TB	143	1091 (35)
8	3	492 (16)	167,995	Recurrent Bacterial Pneumonia	196	423 (15)
6	3	798(20)	160,770	Recurrent Bacterial Pneumonia	31	n/a
5	1	610 (15) #	198,047	Recurrent bacterial Pneumonia	168	301 (12)
9	2	371 (26)	397,826	Recurrent Bacterial Pneumonia	198	334 (26)
3	1	1436 (29)	43,684	Recurrent bacterial Pneumonia	227	835 (15)
6	2	616 (26)	74,125	Recurrent Bacterial Pneumonia	222	570 (18)
8	2	376 (21)	>750000	Chronic lung disease[b]	570	248 (18)
6	2	285 (20)	88,302	Symptomatic LIP~	53	n/a

Enrollment				*Event*		
Age (years)	**WHO Stage**	**CD4 cells/μl (%)**	**HIV RNA copies/ml**	**WHO Stage 3 or 4 Event**	**Event Day***	**Recent CD4 cells/μl (%)†**
8	3	870(26)	32,481	Symptomatic LIP~	528	532 (23)
7	3	775 (13) #	434176	Symptomatic LIP~	30	n/a
6	1	803 (36)	49,543	Thrombocytopenia	252	814 (33)

n/a: no additional laboratory evaluation before event

*Number of days from enrollment

†Most recent laboratory evaluation prior to the event, all within 90 days

^borderline CD4 that rose upon repeat testing

*a*Died after acute onset of right arm pain, left sided weakness and dyspnea; no autopsy was performed

*b*Persistent (>1 month) productive cough, with small cysts and/or persistent opacification on chest x-ray.

~Lymphoid Interstitial Pneumonitis.

#Per WHO and Ugandan guidelines, CD4 count is given preference over % in children over 5 years for ART initiation.

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Table 3

Univariate and Multivariate Cox Proportional Hazard Ratio Modeling of Time to Progression

	Univariate		Multivariate	
Baseline Measure	**HR* (95% CI)**	**p-value**	**HR* (95% CI)**	**p-value**
CD4% (per 10% point decrease)	2.0 (1.8-2.2)	0.005	2.0 (1.8-2.1)	0.013
Log HIV RNA, copies/ml (per unit log increase)	2.4 (1.9-3.0)	0.002	1.8 (1.1-3.2)	0.034
% CD4 Cell Activation^ (per 10% increase)	1.6 (1.5-1.6)	0.05		
% CD8 Cell Activation ^ (per 10% increase)	1.3 (1.3-1.3)	0.05		
Hemoglobin < 9 g/dl	3.1 (1.9-4.3)	0.06		
HIV RNA > 100,000 (c/ml)	2.0 (1.4-2.7)	0.04		
CD4% < 25%	1.6 (0.9-2.3)	0.16		
Male~	2.0 (1.3-2.6)	0.04		
Z-Score Weight-for-Age	0.9 (0.6-1.1)	0.21		
Age (per year increase)	0.9 (0.7-1.0)	0.09		
Age < 3	3.7 (1.7-8.0)	0.001	3.0 (1.3-7.0)	0.008
CD4 count (cells/µl,, per 100 cell increase)	1.0 (1.0-1.0)	0.53		

*Hazard Ratio

^% of cells expressing both CD38+HLADR+

~did not remain significant when adjusted for HIV RNA.

Table 4
Progression Rates based on presence of baseline risk factors

CD4% <25%	HIV RNA >100,000 copies/ml	N =	% Progressed 1-Year*	% Progressed 2-Years*
no	no	55	11%	15%
no	yes	38	16%	21%
yes	no	39	14%	14%
yes	yes	60	29%	34%

*Kaplan-Meir Product-Limit Survival Estimates